FDA QUARTERLY ACTIVITIES REPORT

Fourth Quarter • Fiscal Year 1995
(July • August • September 1995)

Office of Planning and Evaluation
Planning and Management Communications Staff
Program Information and Analysis Group

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

The Last *FDA Quarterly Activities Report (QAR)*

The *QAR* has served the Agency over the last 28 years by reporting Agency accomplishments and highlighting significant Agency activities. Information published in the *QAR* has been provided by representatives of the Agency's various centers, staffs, and field offices. Many are now utilizing FDA's Home Page or specialized publications to report on this same information. A combination of the Agency's expanded use of electronic communications, specialized publications, and diminishing resources brings the *QAR* to its end. This issue, the fourth quarter of FY95, is the last issue of the *QAR*.

Activities information is now available on FDA's Home Page on the Internet World Wide Web and can be reached at the Uniform Resource Locator: http://www.fda.gov/fdahomepage.html

The Office of Regulatory Affairs (ORA) has its own Home Page on the World Wide Web and can be reached at the Uniform Resource Locator: http://www.ora.fda.gov.8000

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Legal Corner

This section summarizes cases that have had, or will have, a significant impact on the regulatory activities of the Agency.

Professionals and Patients for Customized Care v. Shalala. On June 15 a U.S. court of appeals affirmed a district court judgment that an FDA *Compliance Policy Guide (CPG)* concerning the manufacture of drugs by facilities with retail pharmacy licenses is not a substantive rule and therefore is not subject to the notice and comment requirement of the Administrative Procedure Act (APA). In October 1993 the district court had held that the CPG was either an interpretative rule or a policy statement, both of which are exempt from APA requirements. The appellate court held that the CPG did not have a binding effect because the plain language of the guidance did not impose significant new obligations; that FDA had not treated the factors identified in the CPG as establishing binding norms for enforcement proceedings; and that the CPG did not significantly constrain the Agency's discretion because it affords the opportunity for individualized enforcement determinations. (GC)

United States v. International Nutrition, Incorporated. On June 23 a U.S. district court fined the defendant $60,000. In February the defendant had pleaded guilty to misdemeanor violations of distributing unapproved drugs that were promoted for a variety of conditions, including heart disease, epilepsy, and immunological deficiencies. The company's president was also fined $5,000 and sentenced to 5 years of probation. (GC)

Kimball v. FDA. On June 28 a U.S. district court dismissed with prejudice the final claim in this case involving unconstitutional conduct by an FDA employee. On March 28 the court had granted a government motion to dismiss the tort claims of false imprisonment, false arrest, and malicious prosecution. The court had ruled that the sovereign immunity provision of the Federal Tort Claims Act barred those claims. However, the court had also let stand one remaining count, which was dismissed pursuant to a stipulation between the parties. (GC)

National Council for Improved Health v. Shalala. On June 30 a U.S. district court dismissed all three counts of a complaint filed by manufacturers, distributors, and consumers of dietary supplements. The complaint claimed that certain FDA regulations infringed their constitutional rights and were promulgated without statutory authority. On the first count, the court ruled that the plaintiffs failed to state a claim upon which relief could be granted, and that the regulations did not constitute a prior restraint in violation of the First Amendment right to free speech. On the second count, the court held that the plaintiffs failed to specify how or where FDA was attempting to establish potency limits for vitamins and minerals. On the third count, the court concluded that the plaintiffs' challenge to the regulations governing nutrient content claims and nutrition labeling for dietary supplements was premature because FDA had indicated its intent to modify the regulations to comply with the Dietary Supplement Health and Education Act of 1994 and to defer enforcement of the regulations until they are revised. (GC)

United States v. K-V Pharmaceutical Company. On July 17 a U.S. district court sentenced the defendant to 48 months of probation, fined the company $500,000, and ordered the company to pay the government's investigative costs of $100,000. In May the defendant pleaded guilty to misdemeanor violations involving the manufacture and distribution of a pediatric antibiotic prescription drug. The court also sentenced the company's former director of quality assurance to 1 year of probation and fined $250. (GC)

United States v. Two Container Loads ... of Articles of Food. On June 30 a U.S. district court granted the government's motion for summary judgment and condemned imported food from Bangladesh. This civil seizure was a joint enforcement action brought by FDA and the U.S. Fish and Wildlife Service. The complaint alleged violations of the FD&C Act, the Endangered Species Act (ESA), and the Lacey Act. The seized food, labeled as frozen shrimp, also contained a species of frog legs protected under the ESA. FDA analysis detected *salmonella*, a poisonous and deleterious substance, in both products. The claimant (bankrupt Company) argued that it had a statutory right under the FD&C Act to export the food in lieu of forfeiture. The court ruled that even if the statutory provision concerning exports applied, FDA was justified in exercising its discretion and proceeding under another statutory provision authorizing seizure because the claimant had attempted to conceal the frog legs and had a history (including a criminal conviction) of reimporting previously rejected *salmonella*-contaminated shrimp. (GC)

Bristol-Myers Squibb Company v. Shalala. On July 21 a U.S. district court dismissed the third of three cases involving bulk bleomycin sulfate, an antibiotic substance used to manufacture an anticancer drug. The court held that the plaintiff lacked constitutional standing to challenge FDA's position until the Agency actually approved an application for the bulk substance. The court also ruled that until such approval was granted, the plaintiff's claim of competitive injury was not imminent and the allegation of injury was speculative. (GC)

Forsyth v. Eli Lilly & Company. On July 28 a U.S. district court dismissed the complaint against the government and drug manufacturers that FDA had negligently approved Prozac for the treatment of depression. The court ruled that FDA's approval of Prozac was based on the

Agency's primary function of protecting the public health, and that the approval required Agency officials to balance the public's need for new drugs and the public's interest in safe and effective drugs. The court also concluded that the government's actions in approving Prozac were within the scope of the discretionary function exception to the Federal Tort Claims Act and thus that there was no waiver of sovereign immunity and no government liability. (GC)

Stauber v. Shalala. On August 4 a U.S. district court granted FDA's motion for summary judgment upholding the Agency's approval of the new animal drug application for Posilac (recombinant bovine somatotropin), a product that increases milk production in dairy cows. The court ruled that FDA had properly considered animal and human health and safety issues related to the use of the drug. The court also ruled that FDA had properly determined that the drug's packaging label adequately addressed the risks of the drug to dairy cows, and that mandatory labeling for products derived from cows treated with the drug was not necessary. Finally, the court ruled that FDA had complied with the requirements of the National Environmental Policy Act. (GC)

Soucek v. United States. On August 18 a U.S. district court dismissed the case for lack of subject-matter jurisdiction. The plaintiff sought monetary damages and injunctive relief for injuries allegedly caused in 1986 by Halcion, a drug for insomnia. The court ruled that the claim against the government had been filed after the 2–year statute of limitations had run out. The court also ruled that FDA's decision to approve the marketing of Halcion was a discretionary function and thus not subject to liability under the Federal Tort Claims Act. (GC)

A.L. Pharma, Incorporated v. Shalala. On August 25 a U.S. court of appeals affirmed in part, and reversed and remanded in part, the district court's grant of summary judgment for FDA. In a series of four administrative petitions, the plaintiff challenged FDA's approval of a new animal drug application (NADA) filed by a competitor for a product to improve growth and feed efficiency in broiler chickens. The court of appeals ruled that the evidence presented to the district court clearly indicated that FDA did not violate its own regulations. The court also ruled that the administrative record was insufficient because FDA did not provide an adequate explanation for rejecting the plaintiff's criticism that the study used to determine bioequivalence was inappropriate. Thus the court instructed the district court to return the matter to FDA either for reconsideration or for an adequate explanation of the Agency's determination that the study established bioequivalency. Despite its conclusion that the Agency's bioequivalence determination was not satisfactorily explained, the court declined to vacate immediately the NADA approval, and left the rule in place for 90 days to give FDA the opportunity to provide an adequate justification for its decision. (GC)

Cutler v. Hayes. On September 6 a U.S. district court dismissed a challenge to the over-the-counter (OTC) drug review program in a suit that had been pending since 1981. FDA started the program in 1972, to evaluate OTC drugs that are not covered by approved new drug applications. The plaintiffs' suit challenged three aspects of the review:

- FDA's policy of generally not taking enforcement action against a drug while it is under review;
- review procedures that allow testing of ingredients for safety and effectiveness while they are under evaluation; and
- the number of years that the Agency takes to complete the review.

In 1982 the district court ruled for FDA on all three issues. In 1987 the court of appeals upheld the district court on the first two issues but remanded the question of delay for further consideration. On remand, the government presented a detailed report on the status of the review to the court, and in 1988, following additional discovery, the parties filed cross motions for summary judgment. In the latest action, the court dismissed the case with prejudice after the government made a presentation on the accomplishments and current status of the review. (GC)

Who's Where?

This section contains a selected listing of persons who have recently entered or left key Agency positions.

Office of Regulatory Affairs

Richard H. Barnes—Director, Division of Federal-State Relations, Office of Regional Operations; formerly, Director, Consumer Protection Division, Oklahoma State Department of Health.

David L. Chapman—Retired; formerly, District Director, San Francisco District, Pacific Region.

Center for Veterinary Medicine

Mack A. Holt—Acting Director, Office of Animal Care and Use; formerly, Veterinary Medical Officer, Office of Animal Care and Use.

Center for Biologics Evaluation and Research

Thomas G. Bird—Resigned; formerly, Special Assistant to the Deputy Director, Office of Science Policy, Immediate Office of the Director.

David S. Finbloom—Acting Director, Division of Cytokine Biology, Office of Therapeutics Research and Review; formerly, Laboratory Chief, Laboratory of Cytokine Research, Division of Cytokine Biology, Office of Therapeutics Research and Review.

Theresa L. Gerrard—Resigned; formerly, Director, Division of Cytokine Biology, Office of Therapeutics Research and Review.

Jay P. Siegel—Director, Office of Therapeutics Research and Review; formerly, Acting Director, Office of Therapeutics Research and Review.

David E. Wardrop—Deputy Director, Office of Management; formerly, Director, Division of Management and Budget, Office of Management.

Center for Food Safety and Applied Nutrition

Ronald J. Biskup—Retired; formerly, Acting Director, Beltsville Technical Operations Staff.

Paris M. Brickey, Jr.—Deceased; formerly, Director, Division of Microanalytical Evaluations, Office of Plants and Dairy Foods and Beverages.

William B. Carter—Acting Special Assistant, Office of Plants and Dairy Foods and Beverages; formerly, Acting Director, Division of Cooperative Programs, Office of Field Programs.

Darla E. Danford—Director, Division of Science and Applied Technology, Office of Special Nutritionals; formerly, Senior Nutrition Science Advisor, Office of Disease Prevention and Health Promotion, Office of the Assistant Secretary for Health, Department of Health and Human Services.

John N. Hathcock—Resigned; formerly, Director, Division of Science and Applied Technology, Office of Special Nutritionals.

Alan M. Rulis—Director, Office of Premarket Approval; formerly, Acting Director, Office of Premarket Approval.

Patricia S. Schwartz—Acting Deputy Director, Office of Seafood; formerly, Acting Director, Office of Seafood.

Thomas L. Schwarz—Director, Division of Cooperative Programs, Office of Field Programs; formerly, Science Policy Analyst, Executive Operations Staff.

Philip C. Spiller—Acting Director, Office of Seafood; formerly, Special Assistant, Office of Seafood.

Center for Drug Evaluation and Research

Russell J. Abbott—Director, Office of Management; formerly, Director, Office of Management, Center for Biologics Research and Review.

Elizabeth C. Kelly—Retired; formerly, Director, Medical Library, Office of Training and Communications.

Thomas Ludden—Resigned; formerly, Director, Division of Prescription Drug Compliance and Surveillance, Office of Compliance.

Robert C. Nelson—Reassigned to Division of Epidemiology and Surveillance, Office of Epidemiology and Biostatistics; formerly, Director, Division of Training and Development, Office of Training and Communications.

Center for Devices and Radiological Health

Paul R. Beninger—Resigned; formerly, Director, Division of General and Restorative Devices, Office of Device Evaluation.

Gregory Campbell—Director, Division of Biostatistics, Office of Surveillance and Biostatistics; formerly, Chief, Analytical Biometrics Section, Biometry and Field Studies Branch, Clinical Neurosciences Program, Division of Intramural Research, National Institute for Neurological Disorders and Stroke, National Cancer Institute, National Institutes for Health.

Charma Connor—Reassigned to Division of Bioresearch Monitoring, Office of Compliance, CDRH; formerly, Director, Division of Prescription Drug Compliance and Surveillance, Office of Compliance.

Steven I. Gutman—Director, Division of Clinical and Laboratory Devices, Office of Device Evaluation; formerly, Acting Director, Division of Clinical and Laboratory Devices, Office of Device Evaluation.

Larry G. Kessler—Director, Office of Surveillance and Biometrics; formerly, Chief, Applied Research Branch, Division of Cancer Prevention and Control, National Cancer Institute, National Institute of Health.

Karen L. Moss—Director, Division of Program Operations, Office of Compliance; formerly, Acting Director, Division of Program Operations, Office of Compliance.

R. Lakshmi Vishnuvajjala—Mathematical Statistician, Division of Biostatistics, Office of Surveillance and Biostatistics; formerly, Acting Director, Division of Biostatistics, Office of Surveillance and Biostatistics.

Kimber C. Richter—Acting Director, Division of General and Restorative Devices, Office of Device Evaluation; formerly, Deputy Director, Clinical and Review Policy, Office of Device Evaluation.

Program Support

Communications

The Office of Public Affairs (OPA) has continued its work with the Office of Information Resources Management to develop a Home Page on the Internet World Wide Web. The FDA Internet site is being "visited" by the public about 30,000 times a week. (OPA)

Press Releases. The following press releases were issued during the quarter:

Fluoroquinolone Antibiotic for Poultry Approval: On August 18 FDA approved a fluoroquinolone antibiotic, sarafloxacin, for use in poultry drinking water to control illnesses caused by Escherichia coli (E. coli) bacteria. Sarafloxacin is the first fluoroquinolone approved for use in food animals. Fluoroquinolones are the newest class of antibiotics developed for treating infections in people and animals. (For additional information, telephone Donald McLearn on 301–443–1130.)

Patient Education Program: On August 23 FDA proposed a program to give patients, through their pharmacists and other health professionals more and better information about the prescription drugs they use. (For additional information, telephone Donald McLearn on 301–443–1130.)

Informed Consent Proposals for Experimental Therapies: On September 21 FDA proposed ways to make it easier for drugs and medical devices to be studied in patients who are in life-threatening situations and unable to give informed consent for their use. (For additional information, telephone Betsy Adams on 301–443–3285.) (OPA)

Talk Papers. Talk papers were prepared to provide background information and clarification on a number of other FDA-related activities or concerns, including the following:

Standard for Medical Device Wires: On July 5 FDA proposed setting a new performance standard for electrical wires that connect patients to medical devices such as those used to monitor breathing, heart rate, and brain waves. (For additional information, telephone Sharon Snider on 301–443–3285.)

FDA Public Hearing on Autologous Cells: On July 5 FDA discussed its policies on the regulation of products that are composed of living human cells for autologous transplantation, and announced a public hearing, scheduled for November 16–17, to gather comments on these products and services, their public health impact, and various possible regulatory approaches. (For additional information, telephone Lawrence Bachorik on 301–443–1130.)

New Indication for Simvastatin: On July 6 FDA reported that it had been receiving questions about the recent approval of a new indication for Zocor (simvastatin), the first cholesterol-lowering medicine that is indicated for reducing deaths and preventing heart attacks in people with heart disease and high cholesterol. (For additional information, telephone Ivy Kupec on 301–443–3285.)

Treatment for Impotence: On July 6 FDA discussed the approval of self-injected alprostadil to treat impotence. Injectable alprostadil is manufactured by the Upjohn Corporation and will be marketed under the trade name Caverject Sterile Powder. (For additional information, telephone Arthur Whitmore on 301–443–4177.)

Safety of Blood and Blood Products: On July 12 FDA reported that it had received questions about a study on human immunodeficiency virus (HIV) transmission through blood products recently released by the Institute of Medicine (IOM). Changes that FDA has required and encouraged during and since the period studied by IOM have transformed the way U.S. blood and plasma companies operate and are regulated. (For additional information,

FDA said it had received inquiries about recently updated information materials for women who are considering

[redacted]

July 13 the National Institutes of Health (NIH) announced

whole-cell vaccine used in the United States. (For additional information, telephone Lenore Gelb on 301–443–4177.)

TDA and Polyurethane Breast Implants: On June 28 FDA discussed the final results of a study of cancer risks associated with polyurethane foam-covered breast implants, which support FDA's original recommendation that women with polyurethane foam-covered breast implants who are not experiencing problems should not have them removed solely because of concern about cancer from exposure to 2,4–toluenediamine (TDA). (For additional information, telephone Susan Cruzan on 301–443–3285.)

Osteoporosis Drug Approval: On July 13 FDA reported that it had received inquiries about the unanimous vote by FDA's Endocrinologic and Metabolic Drugs Advisory Committee to recommend approval of alendronate sodium (Fosamax) for the treatment of osteoporosis in postmenopausal women. (For additional information, telephone Susan Cruzan on 301–443–3285.)

Drug Abuse Sweat Patch Test: On July 20 FDA cleared the first sweat patch to test for amphetamines, cocaine, and opiates for use in drug abuse screening programs at clinical and rehabilitation centers. (For additional information, telephone Sharon Snider on 301–443–3285.)

Theophylline-Containing Bronchodilators and Ephedrine Drug Products: On July 27 FDA reported that it had received inquiries about its determination that over-the-counter (OTC) combination bronchodilator drug products that contain theophylline are not safe or effective. (For additional information, telephone Ivy Kupec on 301–443–3285.)

New Guidance on Safety of U.S. Blood Supply: On August 10 FDA issued guidance to the blood industry designed to increase the safety of the U.S. blood supply, recommending that blood establishments test donors with new HIV–1 antigen test kits after they become available. The Agency also issued guidance to minimize any risk of transmitting Creutzfeldt-Jakob disease through blood products. (For additional information, telephone Lenore Gelb on 301–443–3285.)

Norplant Update: On August 17 FDA discussed inquiries it had received about the implantable contraceptive drug Norplant and about the ways in which patients and providers receive information on the risks and benefits of the product. (For additional information, telephone Donald McLearn on 301–443–1130.)

New Drug Therapy for Osteoporosis: On August 18 FDA approved calcitonin salmon nasal spray (Miacalcin Nasal Spray) for the treatment of osteoporosis in women, beginning 5 years after menopause. (For additional information, telephone Arthur Whitmore on 301–443–3285.)

FASEB Issues Final Report on MSG: On August 31 the Federation of America Societies for Experimental Biology (FASEB) presented to FDA the final report on its FDA-sponsored review of the safety of the food ingredients monosodium glutamate (MSG) and other free glutamates, which reaffirms the safety of MSG at normally consumed levels for the general population. (For additional information, telephone Larry Bachorik on 301–443–1130.)

Expanded Access to Investigational Treatment for CMV Retinitis: On September 1 FDA authorized treatment investigational new drug (IND) status for intravenous cidofovir (Vistide) for HIV-infected persons with relapsing cytomegalovirus (CMV) retinitis that has progressed despite treatment. (For additional information, telephone Ivy Kupec on 301–443–3285.)

Sale of Thalidomide: On September 7 FDA reported that it had received inquiries about letters to three acquired immunodeficiency syndrome (AIDS) buyers' clubs (organizations that buy products to treat persons with AIDs), warning them to stop their illegal sale of thalidomide. (For additional information, telephone Ivy Kupec on 301–443–3285.)

Suspended Licenses of Utah Blood Bank: On September 8 FDA reported that it had received inquiries about its suspension of the establishment and product licenses of Intermountain Health Care Incorporated's Latter Day Saints Hospital Blood Bank in Salt Lake City. (For additional information, telephone Lenore Gelb on 301–443–3285.)

Approval of Riluzole for ALS: On September 19 FDA's Peripheral and Central Nervous System Drugs Advisory Committee recommended approval of riluzole for patients with amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease. (For additional information, telephone Susan Cruzan on 301–443–3285.)

Eye Laser for Nearsightedness: On September 19 FDA indicated its readiness to approve the first ophthalmic laser, in a procedure called photorefractive keratectomy to correct mild to moderate nearsightedness, in some people who normally use glasses or contact lenses to improve distance vision. (For additional information, telephone Sharon Snider on 301–443–3285.)

ISSC Vibrio Vulnificus Control Plan for Oysters: On September 21 FDA announced that the Interstate Shellfish Sanitation Conference (ISSC) had adopted an interim control plan designed to help reduce the risk of *Vibrio vulnificus* infection from eating raw oysters. (For additional information, telephone Brad Stone on 202–205–4144.)

Expanded Access to Experimental Treatment for Advanced Renal Cell Cancer: On September 26 FDA allowed expanded access to a new technology involving autologous somatic cell therapy for metastatic (stage IV) renal cell cancer. (For additional information, telephone Lenore Gelb on 301–443–3285.)

Liver Stent: On September 29 FDA approved a new, implantable liver stent, a device intended to prevent the recurrence of bleeding from veins in the esophagus in people with cirrhosis, a severe scarring of the liver caused by several different diseases. (For additional information, telephone Sharon Snider on 301–443–3285.) (OPA)

New Consumer Publications Released. Several new consumer information materials were published during the quarter:

- The Communications Staff published the July-August and September 1995 issues of *FDA Consumer* magazine and the July, August, and September issues of the *FDA Today* employee newsletter.
- *Tampering Education.* Public service announcements (PSAs) to educate the public to be alert for signs of product tampering, which FDA developed with the

Council on Family Health (the education arm of the OTC drug industry), appeared in several major consumer magazines. The business edition of *Time* magazine (circulation 1,635,000) included a full-page version of the ad, as did regional issues (circulation 1,356,400) of *Time*. The PSAs were also included in *McCall's* (circulation 4,600,000), *Mature Outlook* (931,813), and for three consecutive weeks in *Parade* (1 million). Total readership for the PSAs has reached 38 million.

Other publications released during the quarter:

- New reprints from FDA Consumer:
  - *Making It Easier to Read Prescriptions*
  - *Public Affairs Specialists: FDA's Walking Encyclopedias*
  - *An FDA Guide to Choosing Medical Treatments*
  - *Keeping Medical Devices Safe From Electromagnetic Interference*
- Revised reprint from FDA Consumer:
  - *Getting Information from FDA*
- Spanish Fact Sheets:
  - *La Nueva Etiqueta De Los Alimentos: Prevencion Contra las Enfermedades del Corazon* (The New Food Label: Help in Preventing Heart Disease)
  - *Abusando De Los Rayos Del Sol* (Hazards of Sun Tanning)
  - *Los Peligros Del Plomo* (The Dangers of Lead)
- Revised FDA Backgrounders:
  - *Monosodium Glutamate*
  - *Milestones in U.S. Food and Drug Law History* (OPA)

Media Activities Continue. The Agency received 524 inquiries from the electronic media, including 167 from television networks (ABC, CBS, NBC, CNN, Fox), 143 from network affiliates, and 69 from radio. The staff arranged on-camera interviews for 11 network appearances and 15 affiliate appearances as well as 18 radio interviews. In addition, the staff arranged briefings for FDA spokespersons in preparation for on-camera interviews. Of the 167 TV network inquiries, 32 were from newsmagazines ("60 Minutes," "Dateline NBC," "PrimeTime Live," "Nightline," "20/20," "First Person," and "48 Hours"); responding to such inquiries required 3 to 5 months of continuous research with producers. (OPA)

Freedom of Information (FOI) Requests. The number of FOI requests that the Agency received during the quarter increased slightly over those in the previous quarter. During the period from July 1 to September 30 a total of 13,272 requests were logged. This is an increase of 325 requests, approximately 3 percent. Denials of FOI requests totaled 136, a 43 percent increase from the previous quarter. (OPA)

Consumer Activities Continue. FDA routinely holds meetings, participates in conferences, and works with consumers and "multiplier groups" to strengthen the public's understanding of and involvement in Agency issues. During the quarter the Office of Consumer Affairs (OCA) organized the following meetings and provided opportunities for consumer participation in the Agency's decision-making process:

- *Advisory Committees:* On August 10 the FDA Consumer Consortium evaluated and recommended nominees for consumer representatives and alternates to serve on the Oncologic Drugs Advisory Committee, Circulatory System Devices Advisory Panel, and the Ear, Nose, and Throat Devices Advisory Panel.
- *Participation:* OCA invited consumer organizations and editors to meetings to participate in the discussion of the new patient education program and the proposed rule to amend current informed-consent regulations.
- OCA distributed the summer *Consumer Quarterly* to 1,500 consumers, consumer organizations, newsletter editors, and women and minority groups, as well as to Center Directors and public affairs specialists. (OCA)

Consumer Inquiries: During the quarter approximately 5,150 people contacted FDA by mail and telephone from around the country, Europe, and Canada seeking information on FDA-regulated products and policies. The issues of highest concern were:

- *Food Labeling:* OCA received more than 1,600 inquiries about the new food label. These included inquiries on how to use the food label to follow a low-fat, low-sodium, or other prescribed diet. Consumers asked for explanations of "sugars" and of the 2,000–calorie basis cited on the label, as well as the definition of percent daily values.
- *Dietary Supplements:* OCA received approximately 800 inquiries about the safety of herbal remedies/dietary supplements.
- *MEDWatch Adverse Event Reporting Program:* OCA received approximately 2,000 calls requesting safety information about FDA-regulated products, particularly dietary supplements and herbal remedies. A few adverse event reports targeted pedicle screws, temporomandibular joint, and breast implants.
- *Tobacco:* OCA received approximately 50 inquiries about the proposed tobacco regulation. Many people requested additional information for research projects. Some said they were glad that the issue has finally come to light, while others expressed opposition to the government's interference.

Other topics of concern were:

- Breast implants,
- eye lasers, and
- investigational and new drug approval processes. (OCA)

Grassroots Partnership Meeting Held. On August 25 the Southwest Region held a grassroots partnership meeting with the medical device industry as a follow-up to an earlier National Performance Review grassroots meeting directed by Vice President Gore. FDA officials have already taken action in response to concerns that industry representatives identified at the meeting. For example, following a request to participate in the generation of guidance

documents, the St. Louis Branch and the Southwest Regional Office arranged for two major ophthalmic companies to cooperate with FDA in a research project on phacoemulsification devices, the ultimate goal of which is to generate a 510(k) guidance document. In addition, the Southwest Regional Office has helped a refurbisher who attended the meeting to present its data and views to the Agency for consideration in the rewriting of FDA's

inspection process. All three districts in the Southwest Region plan further discussions of the specific issues the device industry has raised. (ORA)

Import Inspection Site Opens. Philadelphia District participated in the "United Postal Service (UPS) International Open House" on September 8 in anticipation of the start of operations at its new Courier Hub at Philadelphia International Airport on September 11. U.S. Customs Service and U.S. Department of Agriculture officials also attended. The open house gave UPS managers an opportunity to meet Agency officials, to discuss roll-out dates and to show off the new facility. This major new port in the district will substantially increase the entries of imported FDA-regulated products. (ORA)

Biologics Update '95 Meeting Held. The annual Biologics Update meeting for 1995 took place on July 24–25 in Washington, D.C. The meeting to facilitate communication between FDA and the biologics industry, was sponsored by the Food and Drug Law Institute, in cooperation with the FD&C Law Committee of the American Bar Association's Section of Business Law.

Of special interest was the discussion of the development of CBER performance measures and the drafting of a tissue regulation. (CBER)

CBER Animal Care Program Retains Full Accreditation Status. The American Association for Accreditation of Laboratory Animal Care site visitors have reviewed CBER's animal care program and facilities and recommended continued full accreditation. The full accreditation status assures CBER investigators that their animal research will continue to benefit from high-quality care and facilities, and assures the public that CBER's biomedical research and testing are performed humanely. (CBER)

Congressional Activities

Congressional Testimony. A summary of major congressional testimony for the quarter appears in Appendix 4. (OLA)

Status of Legislation Summarized. The following paragraphs summarize actions taken on major new FDA and related bills introduced in the 104th Congress.

FDA FY 96 Appropriations: The House considered the FY 96 Agriculture appropriations bill (H.R. 1976) the week of July 17. H.R. 1976 contains the following provisions for FDA:

- keeps salaries and expenses at the FY 95 level of $819,071,000;
- increases user fee collections for the Prescription Drug User Fee Act of 1992 (PDUFA) and the 1992 Mam-

$15,350,000 ($2.8 million under the FY 95 level);
- keeps the rental of space at the FY 95 level of $46,294,000; and
- states that none of the PDUFA funds shall be used to develop or establish any authorized user fee program.

On July 21 the House passed, by a vote of 313 to 78, H.R. 1976. With regard to FDA issues, the House agreed to an amendment offered by Representative McIntosh (R-IN) that would keep funding at FY 95 levels for the following FDA offices: the Commissioner, Policy, External Affairs, Health Affairs, Legislative Affairs, Consumer Affairs, Public Affairs, Management and Systems, Planning and Evaluation, and Management. The House defeated an amendment offered by Representative Bunning (R-KY) that would have deleted all FY 96 funding for FDA, and an amendment proposed by Representative Sanders (I-VT-AL) that would have required FDA to conduct research to find a method to test for synthetic bovine somatotropin (BST) in milk.

On September 13 the Senate Appropriations Subcommittee on Agriculture completed markup of H.R. 1976, adding the following language related to FDA to the Senate Appropriations Committee Report of this bill:

- eliminates $7 million the House had earmarked for the field laboratory project at the National Center for Toxicological Research (NCTR);
- deletes the House provision establishing ceilings on full-time-equivalent employees for offices in the Office of the Commissioner (OC), but concurs with the House that staffing and funding for these offices should not exceed FY 95 levels;
- directs FDA to include a detailed breakdown of funding and employment levels of OC offices in the appropriations justification provided to the committee in support of the President's budget;
- provides no funds for the implementation or operation of the cosmetic hotline (directs FDA to expand the existing system for reporting adverse reactions to include cosmetics);
- encourages FDA to increase resources for device approvals;
- directs FDA to make quarterly reports to the committee detailing measures taken, level of resources, and progress made in relation to device approvals;
- directs FDA to operate the Orphan Drug Program at not less than the FY 95 level; and
- directs FDA to withhold any further action to eliminate or consolidate field laboratories until the committee has

an opportunity to review a report being completed by the General Accounting Office on the proposed action.

On September 14 the Senate Appropriations Committee completed markup of H.R. 1976, including the Agriculture Appropriations Subcommittee language in the committee report on the bill and adding the following:

- The committee expects FDA to exercise the authority it has to establish current good manufacturing practice requirements for animal drugs separate from the requirements applicable to drugs for human use.
- The committee understands that FDA will be issuing a new proposed rule requiring food products that contain hydrolyzed proteins and autolyzed yeast extracts to be labeled "contains glutamate". In writing the new proposed rule, the committee urges FDA to consider strongly the potential job loss associated with this rule.

On September 20, by a vote of 95 to 3, the Senate passed H.R. 1976, including amendments offered by Senators Reid (D-NV) and Brown (R-CO) to eliminate appropriated funds for the Board of Tea Experts and to repeal the Tea Importation Act.

On September 28 the Senate and House conferees reached agreement on H.R. 1976, with the following results:

- The conferees added $3.8 million to the buildings and facilities account for the NCTR field lab consolidation project (for a total of $12.15 million). The House had originally funded the consolidation project with $7 million, but the Senate had included no funds for the project.
- The conferees deleted the Senate's repeal of the Tea Importation Act, but the conference bill, however, contains language contributed by the Senate that prohibits FDA from using FY 96 appropriated funds to operate the Board of Tea Experts.
- The conferees restored language from the House bill prohibiting an increase in full-time equivalent (FTE) positions in certain offices in the Office of the Commissioner above the FY 95 level.
- The conferees agreed that language in the Senate report regarding FDA's field office restructuring is not intended to impede consolidation efforts.

Regulations Review: On July 18 the House Committee on Reform and Oversight marked up and reported H.R. 994, which would require federal agencies to review certain existing regulations every 7 years. If a regulation did not meet standards of effectiveness, the Agency would have to modify, consolidate, or terminate it. The committee accepted amendments that raised the threshold to $100 million and would phase out the law in 10 years.

Tax Credits for Orphan/Products: On July 20 Senator Orrin Hatch (R-UT) introduced a bill, cosponsored by Senator Max S. Baucus (D-MT), to amend the Internal Revenue Code of 1986 to make permanent the credit for clinical testing expenses for certain drugs for rare diseases or conditions. The bill was referred to the Committee on Finance.

FY 95 Rescissions: On July 21 the Senate passed H.R. 1944, a bill that would rescind $16.3 billion in funds previously appropriated for FY 95, including $228 million for the FDA headquarters consolidation project in Montgomery County. (However, $56 million remains for headquarters consolidation.) The bill contains language allowing $5 million for FDA to fund a seafood research laboratory. On July 27 the President signed H.R. 1944 (P. L. 104–19).

Regulatory Reform: On July 10–20 the Senate considered S. 343, the "Comprehensive Regulatory Reform Act of 1995." Senate Majority Leader Bob Dole (R-KS) introduced the bill on February 2 as part of the Republican effort to restructure the federal government's regulatory process. The bill is the Senate counterpart to the House omnibus regulatory overhaul measure (H.R. 9), part of the House "Contract With America," which passed on March 3 by a vote of 277 to 141.

S. 343 would require federal agencies to perform detailed cost-benefit analyses, risk assessments, and peer review of proposed major rules—originally defined as those having an expected annual cost to the economy exceeding $50 million, among other subjective criteria. (The House bill sets the "major rule" threshold at $25 million.) During floor debate on July 11 the Senate—by a vote of 53 to 45—approved an amendment to increase the economic threshold to $100 million. However, another amendment, offered by Senators Nunn (D-GA) and Coverdell (R-GA) and adopted on July 10 by a vote of 60 to 36, would require agencies to perform cost-benefit analyses and risk assessment for all regulations expected to have a significant economic impact on a number of small businesses, whether the rules met the $100 million threshold test or not.

The bill also contains a provision aimed specifically at blocking enforcement of the "Delaney clause", a section of the 1958 FD&C Act (P.L. 85–929) that prohibits potentially cancer-causing food additives (including some pesticides in or on processed foods), new animal drugs, or color additives. In addition, this language would have the effect of revising the standard under which the safety of food additives and drugs used in food-producing animals is judged. At present, such products must be shown to be "safe" for consumers, which means "a reasonable certainty of no harm". Under S. 343, however, FDA would have to approve a product for use in food even if it "presents a negligible or insignificant foreseeable risk" to consumers.

After the Senate had considered the complex bill for a week and a half—with Senators Hatch and Johnston (D-LA) the leading supporters of the bill, and Senators Glenn (D-OH) and Levin (D-MI) the leading opponents—Majority Leader Dole tried to cut off debate of S. 343 in three separate cloture votes held July 17, 18, and 20. The votes to invoke cloture were 48 to 46, 53 to 47, and 58 to 40, respectively; all three tallies fell short of the necessary 60 votes.

Senate Republicans defeated an attempt to scale back the measure on July 18 by rejecting a substitute amendment sponsored by Senators John Glenn and John H. Chafee (R-RI). The vote was 48 to 52. The amendment would have limited the ability of courts to review regulations and eliminated the requirement in the bill that would force agencies to consider private-sector petitions to modify or repeal major regulations. Opponents of the Glenn version maintained that the court review section is essential to the bill.

BGH in Milk: On July 20 Representative Sanders, along with 29 cosponsors, introduced two bills related to synthetic BST:

- H.R. 2084 would authorize the Secretary of Agriculture to impose labeling requirements for milk and milk products from cows that have been treated with synthetic bovine growth hormone (BGH), would amend the Agriculture Act of 1949 to require the Agriculture Secretary to reduce the price received by producers for milk that is produced by cows injected with synthetic BGH, and would direct the DHHS Secretary to develop a synthetic BGH residue test. H.R. 2084 was referred to the Committee on Agriculture.
- H.R. 2085 would amend the FD&C Act to require labeling for milk and milk products produced from cows treated with synthetic BGH and would direct the development of a synthetic BGH residue test H.R. 2085 was referred to the Committee on Commerce.

FY 96 Treasury (GSA) Appropriations: On July 12 the House Appropriations Committee approved H.R. 2020, the appropriations bill for FY 96 for the Treasury Department and other agencies, including the General Services Administration (GSA). Of interest to FDA are provisions covering the GSA Federal Buildings Fund. On July 19 Representative Duncan (R-TN) offered an amendment that deleted $65,764,000 for new construction for FDA headquarters consolidation in Montgomery and Prince George's Counties, Phase II from the bill. The amendment passed by a vote of 278 to 146. The House passed H.R. 2020 on July 19 by a vote of 216 to 211.

On July 27 the Senate Appropriations Committee approved H.R. 2020, which contains language providing $87 million for FDA headquarters consolidation in Montgomery and Prince George's counties. On August 5 the Senate passed H.R. 2020.

The Senate agreed to an amendment to H.R. 2020 that limits to 60 days the amount of leave that Senior Executive Service employees may accumulate. The bill also contains regulations prohibiting the sale of tobacco products in vending machines in buildings under federal jurisdiction.

On September 13 Senate and House conferences started negotiations to work out differences on H.R. 2020. The conferees have agreed to appropriate $55 million for FDA headquarters consolidation in Prince George's County. The conferees have not yet reached an agreement on this bill. No date has been scheduled for reconvening the conference.

DHHS FY 96 Appropriations: On July 24 the House Appropriations Committee approved H.R. 2127, the FY 96 DHHS appropriations bill. The bill contains language that prohibits the obligation or expenditure of funds in this act or any other act for the position of Surgeon General of the Public Health Service (PHS). On August 3 the House passed H.R. 2127. The House Appropriations Committee report for H.R. 2127 contains language terminating a National Cancer Institute research grant supporting a study of tobacco industry contributions to political campaigns; the study was intended to determine the nature and extent of tobacco industry influence on state tobacco policymaking. The project specifically compared industry contributions to state legislators with the voting records of those individuals on tobacco control initiatives.

Medicare Bone Mass Measurement Standardization Act of 1995: On August 3 Representative Connie Morella (R-MD) introduced H.R. 2185 and Senator Olympia Snowe (R-ME) introduced S. 1118, the "Medicare Bone Mass Measurement Standardization Act of 1995." The bills would amend Title XVIII of the Social Security Act to provide for coverage of bone mass measurement for certain persons under part B of the Medicare program. S. 1118 has been referred to the Committee on Finance. H.R. 2185 has been referred to the Committee on Commerce and the Committee on Ways and Means.

Ricky Ray Hemophilia Relief Fund Act of 1995: On August 11 Senator Mike DeWine (R-OH) introduced S. 1189, the "Ricky Ray Hemophilia Relief Fund Act of 1995." Senator Bob Graham (R-FL) cosponsored this measure. The bill would provide for compassionate payments of claims for persons with blood-clotting disorders, such as hemophilia, who contracted the human immunodeficiency virus from contaminated blood products. The bill would authorize $1 billion to be appropriated to carry out the program. This bill is a companion measure to H.R. 1023 introduced on February 23 by Representative Porter Goss (R-FL). S. 1189 was referred to the Committee on the Judiciary.

Pesticides: On August 10 Senator Richard Lugar (R-IN) introduced S. 1166, the "Food Quality Protection Act." Representative Bliley (R-VA) introduced H.R. 1627, a companion bill. S. 1166, among other things, would establish a negligible risk standard for pesticide residues on raw and processed foods (eliminating the current Delaney standard for carcinogens); allow benefits to be considered in regulating pesticides; and authorize collection of data to better ensure that pesticide tolerances adequately protect infants and children. The bill would authorize an additional $12 million for DHHS to increase monitoring of pesticide residues. The bill was referred to the Committee on Agriculture, Nutrition, and Forestry.

Tobacco/NASCAR: On September 6 Representative Funderburk (R-NC) and 26 cosponsors introduced H.R. 2265, a bill to prohibit the DHHS Secretary or any other instrumentality of the federal government from regulating tobacco products or tobacco-sponsored advertising used or purchased by the National Association of Stock Car Automobile Racing (NASCAR), its agents or affiliates, or any other professional motor sports association. The bill was referred to the Committee on Commerce.

On September 29 Senator Jesse Helms (R-NC), with Senators Faircloth (R-NC) and Warner (R-VA), introduced S. 1295, companion legislation to H.R. 2265. This bill was referred to the Committee on Commerce, Science, and Transportation.

On September 7 Congressman Payne (D-VA) and 19 cosponsors introduced H.R. 2283, a bill to prohibit the DHHS Secretary from regulating the sale or use of tobacco or tobacco products. This bill was referred to the Committee on Commerce.

On September 18 Senator Hatfield (R-OR), with Senators Harkin (D-IA) and Boxer (D-CA), introduced S. 1251, the National Fund for Health Research Act. The bill would double the tax on cigarettes by imposing an increase of 25 cents a pack, and increase the tax on smokeless tobacco and cigars more than tenfold. Senator Hatfield indicated this would be equivalent to the cigarette tax. The government would use the $4.2 billion raised to increase the National Institutes of Health (NIH) funding (to be distributed in amounts proportionate to the appropriations each institute receives). Although this bill does not directly affect FDA, it is complementary to the proposed rule on tobacco because the increased costs of tobacco products would discourage purchases by minors.

On September 20 Senator Wendell Ford (D-KY) introduced S. 1262, a bill to create legislative restrictions on access to tobacco products that are patterned on the proposed rule but so reduced in scope that they would seem to have virtually no effect on youth access. The bill would amend provisions of the PHS Act that link states' receipt of substance abuse grants to the states' laws prohibiting sale or distribution of tobacco products to persons under age 18, and would provide several restrictions that are weaker than the major elements of the proposed rule. It also would add language to the FD&C Act prohibiting FDA regulation of tobacco products.

On September 29 Representative Scotty Baesler (D-KY) introduced H.R. 2414, the "Youth Smoking Prevention Act of 1995", a bill to establish federal authority to regulate tobacco "as a condition to the receipt by states" of federal substance abuse grants. The bill would link section 1921 PHS grants (substance abuse) to state laws to restrict youth access to tobacco, including a requirement for verification of age at point of sale, fines for underage sale or purchase and for use of fake IDs, retailer supervision of tobacco vending machines and self-service displays, restrictions on distribution of free tobacco and of any tobacco products through the mails; and prohibition on the placement of tobacco brand names on items marketed specifically to children. (Current law requires states to have in effect laws that prohibit sale or distribution to persons under age 18.) H.R. 2414 would prohibit the DHHS Secretary from regulating tobacco under the FD&C Act, the Federal Cigarette Labeling and Advertising Act, or the Comprehensive Smokeless Tobacco Health Education Act, and would require the Secretary to report annually to Congress on actions the states have taken to comply with provisions of this bill. The bill was referred to the Committee on Commerce.

Consumer Access to Prescription Drugs: On August 11 Senator David Pryor (R-AR) introduced S. 1191, the "Consumer Access to Prescription Drugs Act of 1995." Under the bill, the patent expiration date of certain human and animal drugs would be deemed to be the original expiration date where an application for the generic drug had been submitted before June 8, 1995, and a substantial investment had been made before that date. This bill would override the patent expiration date changes made by P.L. 103–465. The bill has been referred to the Committee on Labor and Human Resources.

The Life-Extending and Life-Saving Device Act of 1995: On September 8 Representative Jon Fox (R-PA) introduced a bill to amend the medical device provisions of the FD&C Act. The bill is intended to speed medical devices to the public by easing the current regulations in many areas, such as premarket notification and approval, harmonization of standards, investigational devices, and third-party review. H.R. 2290 was referred to the Committee on Commerce. (OLA)

Federal-State Relations

Partnership Agreements in Georgia Implemented. The Atlanta District has recently entered into two partnership agreements with the state of Georgia's Department of Agriculture to reduce duplication of effort and achieve greater consumer protection for the money spent. The first agreement is with the Plant Food, Feed, and Grain Division to investigate potential contamination of fats and oils sold for animal feed use. Under this partnership agreement, both FDA and the state agency have already made inspections, identified companies for coverage, and collected samples.

The second agreement, with the Division of Consumer Protection, signed on September 22, provides for coordination between the two agencies in planning coverage and conducting inspections in the human food industry in Georgia. (ORA)

Efforts to Increase Partnerships. On July 18–19 representatives of the Northeast Food and Drug Officials Association (NEFDOA) and of the regulatory agencies in the six New England states, plus a representative of the Canadian Health Protection Bureau, met with FDA officials in the FDA office in Stoneham, Massachusetts, to explore partnerships that were in effect nationally and ways in which these

could be tailored to meet local needs. The participants agreed to begin immediately to formally share information. They also identified some potential partnerships and made plans to meet again periodically.

Boston District currently has two active partnerships with the state of Massachusetts that are designed to maximize resources and to prevent duplication of efforts. The first is a partnership with the Massachusetts Department of Public Health to conduct inspections of manufacturers and repackers of medical gases in the state to assure compliance with both federal and state laws. The second partnership is an agreement to cooperate in the collection and analysis of products grown in Massachusetts for pesticide residues. This partnership involves the collection of up to 30 samples of produce grown in Massachusetts, which were different from crops chosen by the Boston District's sampling plans.

FDA signed and completed a partnership agreement with NEFDOA during FY 95 to train the retail food industry in New England in the principles of Hazard Analysis Critical Control Point (HACCP). Five day-and-a-half-long workshops were held throughout New England in Rutland, Vermont; Berlin, Connecticut; Providence, Rhode Island; Stoneham, Massachusetts; and Portsmouth, New Hampshire. Participants in the workshops had the opportunity to develop their own HACCP plans using everyday menu items prepared in their facilities. State regulators also took part in the workshops both as trainees and as facilitators. A total of 120 persons were trained in the principles of HACCP. The workshops were planned and implemented by the senior public affairs specialist and the regional food specialists.

The Boston District of FDA and the Maine Department of Agriculture Food and Rural Resources, Division of Regulation, agreed to collect 25 samples of ready-to-eat seafood for microbiological analysis in conjunction with the inspection of seafood plants under an existing federal-state contract. (ORA)

GAO Reports

During the quarter FDA received one final General Accounting Office (GAO) report. Future information about GAO reports is available from the GAO home page on the Internet World Wide Web at www.gao.gov. Findings of the report issued are summarized below:

Nonprescription Drugs: Value of a Pharmacist-Controlled Class has Yet to Be Demonstrated. This report was requested by Representative John D. Dingell (D-MI), Ranking Minority Member of the House Committee on Commerce who asked GAO:

- to assess the evidence for creating an additional class of drugs in the United States that would not be for sale outside pharmacies but would be available without a physician's prescription, and
- to determine whether there are significant benefits or costs from such a class.

The report also reviews pharmacists' counseling of patients on the use of nonprescription drugs.

GAO found little evidence to support the need to establish a fixed or transitional "pharmacy class" of drugs in the United States at this time. Furthermore, GAO found that available evidence calls into question the premise that the countries having such a class realize major benefits. GAO found that:

- there are no reliable and valid studies examining the effect of various drug distribution systems on overall health and health care system costs;
- although a pharmacy class exists in all 10 foreign countries that were studied, it is not used with any frequency in any of them to facilitate the movement of drugs to sale outside specialized drug outlets;
- the European Union has decided not to impose any particular drug distribution system on its member countries because it found no evidence of the superiority of one system over another;
- there is no clear pattern of increased or decreased access to drugs as nonprescription products where a pharmacy class exists;
- although some people assume that a pharmacy class improves safeguards against drug misuse and abuse, these safeguards are easily circumvented, and studies show that pharmacists' counseling is infrequent and incomplete; and
- experience in Florida with a class of drugs similar to a pharmacy class has not been successful; pharmacists have not regularly prescribed these drugs or followed recordkeeping requirements.

GAO further found that despite the absence of an intermediate class, some of the 14 study drugs are available over the counter in the United States whereas they are restricted to prescription sale in many other countries. Conversely, the United States restricts to prescription sale some drugs that other countries allow to be sold without a prescription but only in a pharmacy class.

More of the 14 drugs were available for sale outside pharmacies in the United States than in any of the other countries. Thus, for general sale, GAO found that the United States has the most accessible system. However, if the criterion is the number of drugs available without a prescription, the United States is somewhere in the middle in terms of accessibility.

The report contained no recommendations to FDA. (OLA)

International Activities

U.S.-European Community Task Force on Biotechnology Research Met. The Fifth Meeting of the U.S.-European Community Task Force on Biotechnology Research was held September 21–22, at the National Science Foundation, Arlington, Virginia. A broad range of biotechnology research activities were discussed, including possible future workshops to cover immunological research related to vaccine development, marine biotechnology, and

new technologies for biotechnology research. The Task Force also sponsored a workshop on neuroinformatics on September 19–20.

The U.S. Biotechnology Research Subcommittee is finalizing a report, "Biotechnology in the 21st Century: New Horizons" covering federal investment in various biotechnology areas, including infrastructure. (FDA-International Working Group [FDA-IWG])

Good Clinical Practices Workshop Held. During September FDA conducted a Good Clinical Practices Workshop in Netanya, Israel. This was the first workshop held under the auspices of the U.S.-Israel Science and Technology Commission (USISTC). The Commission is the result of an agreement between President Clinton and Prime Minister Rabin to promote cooperative science and technology activities between the two countries in the private sector. The biotechnology project of the USISTC seeks to harmonize regulatory requirements between the United States and Israel in the area of pharmaceuticals, biologicals and medical devices. The FDA workshops have also made a significant contribution to regional cooperation between the Ministries of Health in Israel and Jordan, and the Palestinian Health Authorities. (FDA-IWG)

FTAA Met. The first meeting of the Free Trade Area of the Americas (FTAA) Working group on Standards was held in Ottawa on August 31–September 1. The meeting was attended by 33 of the 34 countries of the Western Hemisphere participating in the FTAA. The long-term objective of the group is to work toward harmonization of regulations, voluntary standards, and conformity assessment procedures in the Americas.

The first meeting of the FTAA Working Group on Sanitary and Phytosanitary Measures and the second meeting of the working group on Standards met on September 18–19 in Mexico City. The meeting was attended by 23 of the 34 FTAA member nations and 8 international organizations. The working groups are currently charged with preparing technical recommendations for a meeting of the FTAA Ministers being held in Cartegena, Colombia, in March 1996. (FDA-IWG)

***Listeria monocytogenes* Discussed.** FDA officials represented the U.S. food regulatory agencies during the International Food Safety Conference, *Listeria: State of the Science,* held in Rome, Italy, on June 29–20, 1995. This conference was sponsored by the American Frozen Food Institute, Grocery Manufacturers of America, National Food Processors Association, and the National Fisheries Institute, to provide an opportunity for exchange of current technical information and to aid in harmonization of regulatory policies on *Listeria monocytogenes* in food, especially to prevent technical trade barriers between countries.

Representatives of food regulatory agencies, industry and academia, from North american and Europe, participated in the meeting as presenters, panel members and audience. Listeriosis, the disease, and the prevalence of *L. monocytogenes* in various foods, and the positions of regulatory agencies of North American and European countries and of the International Commission on Microbiological Criteria for Foods were discussed. (FDA-IWG)

Twenty-First Session of the Codex Alimentarius Commission Held. The Codex Alimentarius Commission held its Twenty-First Session at the Food and Agriculture Organization (FAO) Headquarters in Rome July 3–8. The meeting was attended by approximately 430 delegates and advisors representing 94 member countries, and observers from 1 nonmember country and 39 international organizations.

Highlights of the meeting were:

- Procedural revisions to more closely align Codex procedures with those of the World Trade Organization data needs.
- The adoption of the four principles regarding the role of science in the decision making process as proposed by the 1994 Session of the Executive Committee.
- Endorsement of the report of the Joint FAO/WHO [World Health Organization] Expert Consultation on the Application of Risk Analysis to Food Standards Issues, which was held in Geneva, Switzerland March 13–17, 1995.
- Adoption of Veterinary Drug Maximum Residue Levels for 5 growth promoting hormones. (FDA-IWG)

Trilateral "Grassroots" Drugs Met. On September 14–15 FDA officials, the Canadian Drugs Directorate, and DIGECIS (Mexican counterpart organization) met in Syracuse, New York. Discussion topics included:

- new drug review,
- pharmacovigilance/post-market surveillance,
- drug surveillance/compliance,
- research,
- clinical pharmacology/biopharmaceutics, and
- OTC drug products.

Results of this meeting will be presented at the Trilateral Meeting to be held October 30–31, in Ottawa. (FDA-IWG)

Biologics GMP Workshop Held. The Center for Biologics Evaluation and Research (CBER) conducted a week-long workshop on GMPs in Mexico, July 24–28, as part of the ongoing Biologics Work Program between FDA and the Ministry of Health, Mexico. This workshop was enabled by the support and funding of the U. S. Agency for International Development with the objective of enhancing the role of the Children's Vaccine Initiative in Mexico. Three scientists from CBER conducted the workshop, which included lectures as well as on-site instruction. Topics included quality assurance, quality control, animal facility and husbandry standards, validation export and import issues, and the review of standard operating procedures. The workshop was part of an ongoing commitment to engage in training and information exchange between the United States and Mexico. (FDA-IWG)

FDA Laboratories Respond to International Vaccine Requests. In two separate international vaccine incidents that threatened successful immunization programs, CBER's laboratories, in cooperation with assistance from the Center for Drug Evaluation and Research's (CDER's) and the Center for Food Safety and Applied Nutrition's (CFSAN's) laboratories, responded to WHO, Pan American Health Organization (PAHO), and individual countries requests for assistance.

A vial of measles vaccine supplied under the UNICEF Immunization programs was implicated in the deaths of three children in 1 day in Kazakhastan. Urgent requests by WHO for testing to support and epidemiologic investigation were responded to by CBER laboratories with cooperation from CFSAN and CDER (St. Louis) laboratories. Immunization which had been halted was able to be resumed when test results supported the conclusion that improper handling of the vial, and not the vaccine itself, was the likely cause.

In separate incidents in multiple countries, warnings are being given by some church leaders that tetanus vaccines used in immunization programs to reduce the incidence of neonatal tetanus are laced with hormones that can cause sterility. CBER, in cooperation with CDER laboratories, has responded to requests from the Mexican, Philippine, and Nicaraguan governments, WHO, and PAHO, by developing and sharing validating test methods, as well as performing actual testing on some lots, demonstrating no detectable hormones in the vaccines. (FDA-IWG)

Medical and Scientific Affairs

Orphan Drug Products. During this quarter one designated orphan drug product received marketing approval: Amiodarone (trade name Cordarone), sponsored by Wyeth-Ayerst Laboratories, of Philadelphia, Pennsylvania, was approved for the acute treatment and prophylaxis of life-threatening ventricular tachycardia or ventricular fibrillation. The sponsor will have 7 years of exclusive marketing rights for its product beginning on the date of its approval. For FY 95, 27 new studies and 8 competing continuation studies received orphan grant funding. In addition, 31 noncompeting continuation studies received awards, bringing the total amount awarded for all studies for FY 95 to $12,203,000. (OPD)

National AIDS Task Force Conference Held. Approximately 80 health care providers, health educators, advocates, and government agencies participated in the National AIDS (Acquired Immunodeficiency Syndrome) Task Force Conference, held in Orlando, Florida, on September 11–15, 1995. The theme this year, "Taking Fraud to Task," focused on encouraging cooperation among the task forces to develop innovative ways to combat AIDS health fraud.

The Southeast Regional Food and Drug Director presented the opening remarks, and the Deputy Director of FDA's Office of Regional Operations and FDA's Director, Division of Federal-State Relations discussed the status of the task forces. Other topics discussed at the conference included AIDS health fraud education materials, dietary supplements, and telemarketing fraud and the AIDS Epidemic. (ORA)

OIG Reports

During the quarter the Office of Inspector General (OIG) in the Department of Health and Human Services issued one final report on its review of FDA's processing of a new drug application (NDA). The findings of the OIG report are summarized below:

Review of the FDA's Processing of an NDA for Therafectin. OIG conducted a review of FDA's processing of an NDA for Therafectin, a drug developed by Greenwich Pharmaceuticals, Incorporated of Greenwich, Connecticut, for the treatment of rheumatoid arthritis. Representative John D. Dingell (D-MI) requested this review in March 1994 in response to the company's claim that FDA had not followed applicable administrative procedures. FDA had notified the company in September 1993 that it could not approve the NDA because the company had provided inadequate data to demonstrate the drug's effectiveness.

OIG determined that FDA, overall, had properly processed the Therafectin NDA. OIG did note certain administrative shortcomings but found no evidence that these affected the approval status of the Therafectin application. In sum, the company was unable to adequately show—either to FDA or to the Arthritis Advisory Committee—that Therafectin was effective for the treatment of arthritis.

OIG found (as did the Agency when it conducted its own evaluation) that FDA can improve certain administrative procedures to further strengthen the NDA review process. Areas OIG cited as needing improvement include documentation of meetings and discussions, procedures for advisory committee meetings, use of outside consultants, protocol design, and refuse-to-file actions.

OIG made no recommendations to FDA, but did encourage FDA to follow through with its planned actions to strengthen the identified administrative procedures. (OM)

Planning and Administration

Distribution of Agency Personnel. A summary of the Agency's personnel distribution by major organizations (expended to date, projected for fiscal year, and ceiling for fiscal year) is shown in Appendix 6. (OM)

Agency Reorganizations: During the quarter the following reorganizations occurred:

Office of Regulatory Affairs:

- Division of Federal-State Regulations—Division of State Federal Regulations, Office of the Regional Operations reorganized the State Information Branch and the State

Program Coordination Branch into a State Contracts Staff and a State Information Staff. In addition, the former Consumer Affairs Information Staff merged with the Division of Federal-State Regulations and was renamed the Public Affairs and Health Fraud Staff.

- New Jersey District Office—The Mid-Atlantic Region District Office charged the name of the Newark District Office to the New Jersey District Office.
- Florida District Office—The Southeast Region changed the name of the Orlando District Office to the Florida District Office.

Center for Drug Evaluation and Research:

- Office of Training and Communications—CDER established the Office of Training and Communications to oversee, coordinate, manage, and evaluate CDER's professional training and communications within CDER and with the other Centers.
- Executive Operations Staff—CDER reorganized the Office of the Center Director to enhance its responsiveness to its internal and external customers and established the Executive Operations Staff to combine project management, executive secretariat, and program management functions. CDER transferred the functions and staff of the Division of Regulatory Affairs from the Office of Compliance to the Office of the Center Director, as the Regulations Policy Staff.
- Office of Compliance—CDER reorganized the Health Fraud Staff, formerly in this Office, was abolished and its functions transferred to the new Division of Labeling and Nonprescription Drug Compliance; established the Division of Prescription Drug Compliance and Surveillance and the Division of Labeling and Nonprescription Drug Compliance; the Case Management and Guidance Branch and the Investigations and Preapproval Compliance Branch transferred to the Division of Manufacturing and Product Quality; and the Clinical Investigations Branch and the Nonclinical Laboratory Studies Branch transferred to the Division of Scientific Investigations.
- Office of Management—The Program Management Services Branch and the Facilities Management Branch are now located in the Division of Management Services.
- Office of Pharmaceutical Science and the Office of Review Management—CDER established the Office of Pharmaceutical Science and the Office of Review Management to realign CDER's major human drug program functions into two primary areas.
  - The Office of Pharmaceutical Science will handle pharmacological, biopharmaceutical, and generic drug reviews. The chemistry review functions have moved to the Office of New Drug Chemistry within the Office of Pharmaceutical Science. The Office of Pharmaceutical Science consists of three staffs (the Chemistry Policy Staff, the Formulations Research Staff, and the Operations Staff) and four Offices (the Office of Clinical Pharmacology and Biopharmaceutics, Office of Generic Drugs, Office of New Drug Chemistry, and Office of Testing and Research).
  - The Office consists of one staff (the Advisors and Consultants Staff) and six offices (the Office of Drug Evaluation I, Office of Drug Evaluation II, Office of Drug Evaluation III, Office of Drug Evaluation IV, Office of Drug Evaluation V, and the Office of Epidemiology and Biostatistics).
  - The new Office of Review Management will align the drug review components into smaller, more cohesive offices to allow a more efficient review process and facilitate communication both up and down organizational lines.

Center for Biologics Evaluation and Research:

- Office of Compliance—The Division of Bioresearch Monitoring and Regulations has become the Division of Regulations and Policy. The Bioresearch Monitoring function is now located in the Division of Inspections and Surveillance.
- Office of Therapeutics Research and Review—The Division of Clinical Trials Design and Analysis has been reorganized to provide more efficient oversight of INDs for therapeutic groups of products. In addition to the Division's Oncology Branch and Pharmacology and Toxicology Branch, the newly designated branches are the Immunology and Infectious Disease Branch (IID) and the Medicine Branch.
- Division of Biostatistics and Epidemiology—CBER reorganized the Division of Biostatistics and Epidemiology to combine the Adverse Experience Branch and the Epidemiology Staff into the Epidemiology Branch. This merger will improve coordination and implementation of the epidemiologic program.

Center for Devices and Radiological Health:

- Office of Systems and Management—CDRH merged the Office of Information Systems and the Office of Management Services and incorporated their functions into the new Office of Systems and Management, established to support CDRH's central management. (OM/CBER)

Regulatory Activities

Agency Field Activities. A summary of the Agency's field activities (inspections, samples analyzed, and wharf examinations) for the quarter appears in Appendix 1. (ORA)

Enforcement Data. A summary of the Agency's enforcement data (seizures, recalls, warning letters, prosecutions, and injunctions) for the quarter appears in Appendices 2 and 3. (ORA).

***Federal Register* Documents.** From July 1 through September 30, the Agency published 184 documents in the *Federal Register.* Among those were 44 on human drugs, 37 on food additives, and 26 on new animal drugs. A listing of notices, proposed rules, and regulations published in the *Federal Register* this quarter appears in Appendix 5. (OP)

Animal Drugs and Feeds

Monitoring of Marketed Animal Drugs, Feeds and Devices

Court Issues Opinion on Live Animals. Recently a U.S. district court issued an opinion that live swine intended for slaughter and subsequent use as food are "food". This decision was issued in response to a motion by Tuente Livestock et al to dismiss certain charges made in a motion for preliminary injunction by the government.

The defendants in this case, Tuente Livestock, Ronald W. Tuente, and Roger B. Tuente, purchase hogs from producers and sell them to slaughterhouses that then slaughter and process the animals for consumption. FDA accused the defendants of delivering to the slaughterhouses swine with illegal levels of the animal drug sulfamethazine. The defendants sought to have the suit dismissed, arguing that live swine are not "food" within the meaning of the FD&C Act. They also stated that they did not engage in the introduction, or the delivery for introduction, into interstate commerce the hogs that were purchased from producers and sold to slaughterhouses.

The court ruled that the term food is ambiguous in the act and that the law does not directly speak to the issue of live animals. Also, the judge stated his opinion that FDA has not published regulations saying that food includes live animals raised for food and intended to be offered for slaughter. The judge added, however, that the position that live animals are food is supported by historical Agency practice, noting that FDA began to take enforcement action against the purveyors of live animals as long ago as 1970. For approximately 15 years the FDA has held the position that offering for slaughter live animals whose edible tissues contain above-tolerance residues exposes the offeror to liability for introducing adulterated food into interstate commerce. In addition, FDA has taken action against other purveyors of live animals in accordance with that position. The judge also stated his belief that the intent of Congress was to permit FDA to reach persons originally responsible for the adulteration of food, which may be those persons who deal with the animals prior to slaughter.

The court concluded that in light of the structure and legislative history of the act, it is permissible for FDA to interpret the term food to include live animals raised for food and intended to be offered for slaughter. The court also concluded that Congress has directly indicated that a party who has purchased an adulterated article from another party and who passes it on to yet another may be held liable under the FD&C Act for introduction of the animals into interstate commerce. (CVM/ORA)

FDA Issues Policy Letter on Generic Drugs. Recently FDA issued the ninth in a series of policy letters on the implementation of the generic Animal Drug and Patent Term Restoration Act, which was signed into law on November 16, 1988. This letter introduced a revised policy statement on the environmental review of generic animal drugs, eliminating the routine requirement for an environmental assessment (EA), and requiring the submission of a request for categorical exclusion under Title 21, *CFR* 25.24(d)(1), for an abbreviated new animal drug application (ANADA).

FDA originally set forth the requirement for the submission of an EA for the finished and bulk manufacturing sites for the production of a generic product.

Since issuing a policy letter, FDA has reviewed more than 100 EAs for generic animal drug products. With few exceptions, the Agency has prepared findings of no significant impact for the manufacture of these generic animal drug products. Because FDA has identified no significant environmental impacts from the manufacturing of generic animal products, the Agency has decided that an EA will no longer routinely be required for ANADAs. Under the new policy, an ANADA submitted for an animal drug product ordinarily must include a request for categorical exclusion from the preparation of an EA under Title 21, CFR 25.24(d)(1). FDA will review the request for categorical exclusion and determine whether the criteria listed for exclusion are met. If they are, and the Agency has no information available to establish that the proposed action may significantly affect the environment, FDA will granted the categorical exclusion. If FDA finds, or a sponsor determines, that the categorical exclusion does not apply, or information indicates that the proposed action may significantly affect the environment, FDA will require an EA for the action.

FDA welcomes comments on the policy statement. If any changes are made, the revised statement will be placed on public display, and a notice of its availability will be published in the *Federal Register.* Comments on the policy statement should be sent to the following address:

Dockets Management Branch
Docket No. 88N 0394
HFA–305, Room 4–62
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Copies of the ninth policy letter and the revised policy statement are available from the *FDA Veterinarian.* (CVM)

Hogan's Dairy Injunction. On July 5 in a U.S. district court, David L. Hogan, owner of Hogan's Misty Meadow Dairy, of Tillamook, Oregon, signed a consent decree of permanent injunction permanently restraining and enjoining him from introducing or delivering for introduction into interstate commerce any cattle intended to be slaughtered for use as food or any edible tissues of cattle unless medicated cows and bulls are identified, medicated in accordance with approved labeling, and held for the proper withdrawal period. The injunction also requires Hogan to segregate the calves intended for sale into a separate pen and to mark medicated calves or calves fed colostrum or

milk from a medicated cow, to use medication in accordance with its approved labeling, to follow withdrawal periods, and to keep written records. The dairy primarily produces fluid milk (36,000 pounds per day); it has a producing herd of 700 cows out of a total herd of 850 adult animals. The farm also has about 850 replacement calves in different stages of growth on hand. The farm annually produces approximately 450 bull calves, which are sold to the veal trade. The injunction recommendation was based on 16 residue incidents in veal between March 1990 and June 1994. USDA analysis of samples of tissue taken from the kidneys of cull dairy calves sold by Hogan and collected at the time of slaughter found residues of streptomycin up to 1,182 parts per million (ppm), neomycin residues up to 641 ppm, and gentamicin up to 48 ppm. The tolerances FDA has set for these antibiotics in calves' kidney tissue are 2.0 ppm streptomycin and 0.25 ppm neomycin; there is no tolerance for gentamicin because the drug is not approved for use in cattle or calves.

This injunction was Seattle District's first tissue residue injunction in Oregon. (CVM)

Pre-Approval Evaluation of Animal Drugs and Food Additives

FDA's Position on the Extra-label Use of Fluoroquinolones. On August 18 FDA approved a new fluoroquinolone antibacterial drug, sarafloxacin, for use in chickens and turkeys. Sarafloxacin, the first fluoroquinolone approved for use in food-producing animals, is a prescription drug distributed under the trade name Saraflox WSP by Abbott Laboratories, North Chicago, Illinois. Saraflox WSP is administered in drinking water for use in broiler chickens and growing turkeys for the control of mortality associated with *Escherichia coli (E.coli)* organisms susceptible to sarafloxacin.

Fluoroquinolones are the newest class of antimicrobial drugs developed for treating infections in people and animals. On May 11–12 the advisory committee of the Center for Veterinary Medicine (CVM) and the Center for Drug Evaluation and Research's Division of Anti-infective Drugs heard presentations from human and animal health researchers and food-animal producers relative to concerns raised about the development of bacterial resistance to fluoroquinolones. Members of both committees concluded that FDA could approve fluoroquinolones found to be safe and effective for animal use.

FDA is eager to preserve the usefulness of this valuable new drug and other fluoroquinolones by minimizing the potential for development of resistant pathogens. To achieve this objective, FDA believes it will be necessary to control unnecessary treatment of animals with fluoroquinolones. Hence FDA is initiating an educational program to inform veterinarians and producers about the appropriate use of fluoroquinolones, and is revising the *Compliance Policy Guide 7125.06,* "Extra-label Use of Animal Drugs in Food-Producing Animals," to include regulatory guidance for these drugs.

FDA will assign a regulatory priority in accordance with the actual use of this class of drugs. The highest priority for regulatory action will be for extra-label use of fluoroquinolones in major food-producing animal species and in classes of species that are not the subject of the approved labeling. A lesser regulatory priority will apply to extra-label use of fluoroquinolones in minor food-producing species or within a major food-producing species or class for which the drug is approved but for which the actual use is not included in the approved labeling of the drug. As defined in Title 21 CFR 514.1(d)(1)(ii), major species include cattle, horses, swine, chickens, turkeys, dogs, and cats; all other species are considered minor species.

FDA is working with the U.S. Department of Agriculture (USDA) and the Centers for Disease Control and Prevention (CDC) to develop a surveillance system to monitor antimicrobial resistance in enteric pathogens. Under the program, USDA periodically will test *Salmonella* samples from animals for continued susceptibility to antimicrobial drug products. CDC will conduct similar testing on samples of human *Salmonella* and *E. coli.* The manufacturer, Abbott Laboratories, will test samples of animal *E. coli* to measure the emergence of any resistance in the drug's target organism. As part of its annual Drug Experience Reports, the manufacturer will also give FDA information on the geographical distribution of the drug. FDA will use the information from the monitoring programs to assess the development of antibiotic-resistant organisms and to make any adjustments in the regulatory program.

People with questions about CVM's position on the extra-label drug use of fluoroquinolones may write to CVM's Office of Surveillance and Compliance at 7500 Standish Place, HFV–200, Rockville, Maryland 20855, or telephone (301) 594–1761. (CVM)

Biologics

Blood and Blood Products

Blood Industry Guidance Issued. On August 8 the Agency issued guidance documents to the blood industry to increase the safety of the U.S. blood supply. Under the new guidance, FDA recommends that blood establishments test donors with new human immunodeficiency virus (HIV–1) antigen test kits after they become available, to further reduce the risk of infecting blood recipients through contaminated transfusions. (A talk paper was released on August 10, 1995; telephone 301–443–3285 for copies.) (CBER)

Antigen Assay Approvable Letter Issued. The Agency issued an approvable letter to the Coulter Corporation,

Miami, Florida, for its Coulter HIV–1 p24 Antigen Assay and Antigen Neutralization Kit intended for use in diagnosis and screening of blood donors. Some labeling issues must be resolved before FDA issues the product license and Coulter may not market the kit until it is licensed. On August 7 FDA gave permission to make public the issuance of the approvable letter. (CBER)

Meeting on Use of Umbilical Cord Blood Held. On August 9 representatives of FDA and the National Heart, Lung, and Blood Institute (NHLBI) met to discuss NHLBI's request to conduct a 5–year study on the use of umbilical cord blood as bone marrow reconstitution for both children and adults with malignancies and immunodeficiencies. FDA and NHLBI are also considering sponsoring joint workshops during the coming year. (CBER)

Blood Bank Licenses Suspended. On September 8 the Agency suspended the establishment and product licenses of Intermountain Health Care Incorporated's Latter Day Saints Hospital Blood Bank in Salt Lake City. The suspension prohibits LDS from shipping blood and blood components interstate. (A Talk Paper was released on September 8, 1995; telephone 301–443–3285 for copies.) (CBER)

Blood Test Licensed. In September FDA approved a license application for Cambridge Biotech Corporation's human T-cell lymphotropic virus, type I (HTLV–I) (rp21e enhanced) enzyme immunoassay. This test is an in vitro enzyme immunoassay for the qualitative detection of antibody to HTLV–I in human serum or plasma. (CBER)

Therapeutic Products

Treatment Protocol Granted for Somatic Cell Therapy. On September 15 FDA allowed a treatment protocol for somatic cell therapy for the treatment of metastatic (stage IV) renal cell carcinoma to proceed. This is the first treatment protocol submitted for somatic cell therapy in which living cells are processed outside the body and used to prevent, diagnose, or treat disease or injuries. (A Talk Paper was released on September 26, 1995; telephone 301–443–3285 for copies.) (CBER)

Meeting of Biological Response Modifiers Advisory Committee Held. At a meeting held on July 13–14 in Bethesda, Maryland, the committee considered the draft guideline "PHS Considerations in Xenotransplantation." FDA and the Centers for Disease Control and Prevention developed the draft guideline, with the National Institutes of Health, Health Resources and Services Administration, Department of Defense, and the Department of Agriculture.

Committee members agreed that the guidelines should be developed and published in response to public health concerns raised by xenotransplantation. These concerns relate to the possibility of inadvertent cross-species transmission of infectious agents, primarily viruses, and the potential introduction of novel viruses into the transplant recipient and the human population through viral adaptation resulting in altered pathogenicity. The guideline deals with xenotransplanted cells and tissues as well as solid organs.

The advisory committee also discussed the public health risks and the rationale of the baboon bone marrow transplantation protocol, which was submitted to FDA. The aim of the protocol was use of baboon bone marrow stem cells to reconstitute the immune system of a patient with advanced HIV disease. The committee voted to allow the protocol for this one patient to proceed with revisions to the consent form that would state the public health risks, the need for the patient to stay in the geographic area where the transplant was performed, and the requirement for long-term follow-up. (CBER)

Food and Cosmetics

Chemical Safety of Foods

Trends in Food-Handling Practices Changing. During the quarter FDA completed the fourth paper in a series on the results of the 1993 Food Safety Survey, titled "Trends in Safety of Food-Handling Practices, Levels of Concern about Food Safety, and Sources of Food Safety Information, 1988 to 1993." A representative sample of more than 1,600 consumers participated in the 1993 telephone survey. The paper reports the following trends that interest food safety educators and regulators:

- Despite an apparent increase in concern about food safety problems, consumers' food-handling practices are deteriorating.
- At the same time, consumers report less reliance on traditional sources of food safety information, particularly the government and food stores.

These trends reflect the changing character of food preparation and the influence of news stories that emphasize gaps and breakdown in the food safety system. The paper raises the importance of educational efforts to improve the public's food-handling practices. (ORA)

Outbreak of *E. Coli* Reported in Montana. On July 21, Montana state and Missoula city health officials notified Seattle District of an outbreak of *Escherichia coli (E. coli)* illness in the Missoula area affected 32 persons, of which 11 had been hospitalized. The number of cases was later revised to 113, of which 30 were confirmed a *E. coli 0157:H7*. When a preliminary investigation pointed to lettuce as the suspected source of the infection, the Missoula City Health Department investigated a local grower of organically grown lettuce. The Seattle laboratory tested 21 samples of lettuce, manure, and compost from the grower's fields, another 35 samples of assorted vegetables

from the grocer that sold the lettuce and samples of bean sprouts, all of which were found to be negative for *E. coli 0157:H7*. (ORA)

Adulterated Frozen Orange Juice from Mexico Found. During a recent routine follow-up of a consumer complaint, investigators from the Spokane, Washington, Resident Post learned that a local plant had received shipments of adulterated frozen orange juice for manufacturing from a supplier in Monterey, Mexico. After receiving two consumer complaints, the company analyzed the orange juice and found high bacterial growth of *Lactobacillus* and diacetyl. The bacteria were apparently surviving the company's pasteurization process, and the product was "erupting" as it approached the expiration date. Although no apparent health hazard is associated with *Lactobacillus,* the bacterium releases diacetyl, which can be identified by a "petroleum"—like odor.

FDA analysis did not confirm the presence of *Lactobacillus* or diacetyl, but did find an indication that the juice may have been adulterated because the simple sugar profile and the Brix value were not typical for single-strength orange juice. The company conducted two recalls as a result of its analyses and returned several hundred barrels of the product to the Mexican supplier. The firm was also aware of that other orange juice manufacturers had experienced similar problems.

FDA issued an import alert on September 22 to alert districts to shipments from the Mexican companies supplying the suspect orange juice. (ORA)

Shippers of Adulterated Crabmeat Sentenced. On September 15 a magistrate judge sentenced Cypress Seafood Processors, Incorporated, of Abbeville, Louisiana, and the company's president, Bethel Dyson, to pay fines and assessments totaling $5,950 after they pleaded guilty to three counts of shipping adulterated crabmeat in interstate commerce. The judge also placed the defendants on supervised probation for 3 years, during which time Dyson will be required to meet all FDA's standard requirements in connection with any future seafood processing business or operations.

The company has long history of processing crabmeat under insanitary conditions. Despite the issuance of a warning letter and two hearings under section 305 of the FD&C Act, the company continued to operate under horrible conditions, and prosecution was recommended in early 1994. (ORA)

Cosmetics Safety and Labeling

Automated Cosmetic Information Line Tested Internally. During the quarter FDA public affairs specialists (PASs) across the country tested the new cosmetic information line, which was developed in response to an increased number of questions from the public on cosmetic topics. The PASs reviewed and commented on the content and quality of the recorded messages and the delivery system so that FDA could identify and correct potential problems before opening the toll-free automated system to the public. The internal testing phase ended on September 30. (For additional information, see *Congressional Activities [FDA FY 96 Appropriations].)* (CFSAN)

Microbiological Safety and Foods

FDA and USDA Sponsor Video-Teleconference on Foodborne Diseases. On July 11 FDA and the U.S. Department of Agriculture (USDA) sponsored a video-teleconference on foodborne diseases to inform state and local health and regulatory officials about recent FDA/USDA regulatory initiatives, Hazard Analysis Critical Control Point (HACCP), and the Food Code. Panelists discussed the education initiatives for high-risk populations, and representatives from USDA, FDA, state and local regulatory agencies, and industry discussed their experience with foodborne diseases. It is estimated that the broadcast reached more than 3,000 viewers, who had the opportunity to call in their questions to the panelists. (CFSAN)

***Vibrio vulnificus* Education Campaign Begun.** FDA recently published a brochure describing who is at risk of acquiring *Vibrio vulnificus* infections from consuming raw oysters and how those hazards can be reduced. The brochure will be distributed through health and medical channels and will be available to the public through the FDA Seafood Hotline. (CFSAN)

Tuna Guidelines Revised. A notice of availability for *Revised Compliance Guide (CPG) 7108.24—Decomposition and Histamine—Raw, Frozen Tuna and Mahi-Mahi; Canned Tuna; and Related Species* was published on August 3, 1995. The revised *CPG* lowers the defect action level (DAL) for histamine and deletes the requirements for organoleptic corroboration for canned tuna. In addition, the *CPG* extends the DAL to raw and frozen tuna, mahi-mahi, and other species implicated in histamine poisoning. At sufficiently high levels, histamine causes the illness called scombriod poisoning. The 1991 report on seafood safety by the National Academy of Sciences' Institute of Medicine listed histamine as one of the three major natural toxins associated with seafood. (CFSAN)

International Workshop on Seafood Decomposition Held. FDA and the Canadian Department of Fisheries and Oceans held an International Seafood Decomposition Workshop on September 18–29 in Gainesville, Florida. The workshop was open to major trading partners of the United States and Canada engaged in exporting shrimp and tuna. Workshop participants examined canned tuna during the first week and shrimp during second. (CFSAN)

Seafood Page Established the WWW. On September 1 CFSAN established a Seafood Page on its World Wide Web (WWW) server which includes the *Regulatory Fish*

Encyclopedia and the *FDA Seafood List* (in a searchable format with links to the *Regulatory Fish Encyclopedia*).

The *Regulatory Fish Encyclopedia* is a joint project of CFSAN and the Seattle and San Francisco districts. The *Regulatory Fish Encyclopedia* was developed to help federal, state, and local officials and purchasers of seafood identify species substitution and economic deception in the marketplace. For 27 of the more frequently consumed fish, the *Regulatory Fish Encyclopedia* on the WWW includes:

- a color photo of the fish and its fillet for visual identification;
- information on its morphological features (key measurements), its geographical distribution, and other available reference material; and
- biochemical gel banding pattern data in a visual and data format.

The CFSAN WWW Seafood Page also contains information from the *Bad Bug Book* on seafood-related foodborne pathogens and toxins (with links to relevant Centers for Disease Control and Prevention [CDC] and USDA documents), among other information of interest to consumers and industry. The Web site is http://vm.cfsan.fda.gov/seafood1.html. (CFSAN/ORA)

European Union (EU) may require that U.S. fish and fishery product processors who wish to ship their products

Currently, the EU accepts EU Health Certificates for [illegible] of product shipments from U.S. companies, provided the seafood processor is on FDA's approved list. The health certificates are a temporary requirement. Controls based on a HACCP system will meet the EU's equivalency requirement. Although HACCP regulations will be published within the next few months, some seafood processors already operate under control of a HACCP program.

A Baltimore District investigator, accompanied by two representatives from CFSAN's Office of Seafood, visited two companies on the Chesapeake Bay's Eastern Shore—a processor of soft crabs, and a processor of clams, shrimp, scallops, and crab cakes—to determine what effect the HACCP programs have had on these companies. Both companies are on FDA's accepted list for EU Health Certificates and have HACCP plans in place. Both endorsed the HACCP concept.

Following these initial visits, Baltimore District and Office of Seafood officials escorted visitors from the Executive Office of the President, Office of Management and Budget (OMB), and FDA's Office of Policy on a visit to the same companies. The purpose of the second visit was to show OMB and FDA's policy advisers how HACCP has affected operations at these seafood processors. (ORA)

***Listeria Monocytogenes* in Imported Processed Seafoods Continues to Be Found.** Recently microbiologists from the Winchester Engineering and Analytic Center found the foodborne pathogen *Listeria monocytogenes* in a variety of [illegible] ready-to-eat seafood product samples (lobster meat and crabmeat) taken from products entering this country from Canada tested positive for this organism. *Listeria monocytogenes* is potentially [illegible] can also cause vomiting, diarrhea, and other gastrointestinal symptoms. *Listeria monocytogenes* thrives in raw milk and cheese, raw and cooked poultry, raw meats, and raw and smoked fish. The bacteria grow at low temperatures and are not easily killed by heat. (ORA)

Human Drugs

Drug Quality Assurance

Warning Letter Issued. On February 8 citing unapproved new drug and drug misbranding charges under the FD&C Act, FDA issued a warning letter to the 3M Company concerning its product DuraPrep, marketed by the company as an over-the-counter (OTC) patient preoperative skin preparation. At a meeting on August 31 FDA advised 3M [illegible] further regulatory action. On September 6 company officials telephoned [illegible] to report that the company would discontinue marketing the present formulation, would reformulate the product with ingredients deferred to further review, and would seek Agency approval of the iodophor-complex through the appropriate means. A meeting was scheduled to discuss this action in detail. (CDER)

Oxygen and Nitrogen Seized. Recently FDA approved a seizure of Oxygen USP and Nitrogen USP at Lincoln Big Three, Incorporated, of Harvey, Louisiana, charging violations of current good manufacturing practices (GMP), adulteration, and misbranding. Major deficiencies included inadequate testing of the products. In July-August 1995 inspectors found that the company had resumed the gas-filling operations that had been suspended following a violative inspection in 1990 without correcting the deficiencies. (CDER)

Electronic Warning Letters Approved. FDA has drafted a [illegible] warning letters which include misbranding charges and seizures. Only the evidence/documentation will be sent in for review. In September 1995 FDA approved two warning letters containing misbranding charges under the pilot program. (CDER)

Thalidomide Warning Letters Issued. On September 1 FDA issued warning letters to three buyers' clubs (Healing Alternatives Foundation, LifeLink, and PWA Health Group) to stop the distribution of the unapproved new drug

thalidomide for the treatment of body wasting. Division of Prescription Drug Compliance and Surveillance will handle any responses to the warning letters. (CDER)

Civil Money Penalties Final Rule. A new final rule, Part 17 of the CFR, concerning the imposition of civil money penalties under five laws enforced by FDA appeared July 27 in the *Federal Register*, and became effective on August 28. The Prescription Drug Marketing Act is one of the laws containing civil money penalty provisions.

FDA participated in the Civil Money Penalties Task Force, which reviewed and commented on the proposed final rule and drafted a new *Regulatory Procedures Manual* to provide guidance to the field offices in the preparation of civil money penalty recommendations under each of the laws containing such provisions. (CDER)

Diversion Scheme Results in Indictment. On July 25 a Newark federal grand jury indicted three persons for their alleged roles in "false export" diversion schemes under which four American manufacturers of prescription drugs, medical devices, and consumer goods suffered millions of dollars in losses. The 122-count indictment includes charges of conspiracy and fraud. FDA's Office of Criminal Investigations participated in the interagency investigation. (CDER)

Digoxin Certification Program Monitored. FDA administers the Digoxin Certification Program established under 21 CFR 210.500, using analytical services provided by the Office of Research Resources in St. Louis, Missouri. On the basis of analytical evidence, on July 20 FDA advised Amide Pharmaceuticals of Little Falls, New Jersey, and Jerome Stevens Pharmaceuticals of Bohemia, New York, that they were no longer required to submit digoxin samples for certification testing for those strengths previously tested and found acceptable. (CDER)

Consent Agreement Signed. On March 12 Forest Tennant, M.D., Director of Community Health Medical Projects (CHP) narcotics treatment program, signed a consent agreement for his 22 California methadone clinics. The agreement requires CHP to establish quality assurance and training programs and $100,000 escrow fund for follow-up inspections and to secure the services of outside experts to certify that his clinics are in compliance with federal, state, and local laws pertaining to narcotic treatment programs. This agreement was the culmination of a 1-year investigation, during which FDA officials found that CHP failed to properly authorize and document methadone changes, conduct counseling, minimize false drug test collections, and review test results.

FDA learned about the problems at CHP clinics in March 1994 through a letter from two former CHP employees. FDA conducted inspections at nine of the clinics sponsored by CHP, and, in June 1994, sent Tennant a warning letter about violations pertaining to medical orders, recordkeeping, treatment plans, urinalyses, patient testing, and counseling. The inspectors had also found that CHP clinics endangered patients by placing them on many concomitant medication protocols and providing ancillary sedatives.

Between October and December 1994 FDA reinspected two of the clinics and performed new inspections of two additional CHP-operated clinics. These inspections revealed continuing deviations from the federal narcotic treatment program regulations similar to those uncovered during the original nine inspections.

On March 13, 1995, FDA notified Tennant that the Agency was going to seek revocation of approval of the violative CHP narcotic treatment programs, and scheduled an informal conference with him for March 21 at which time Tennant signed the consent agreement. If CHP should fail to comply with the terms of the agreement (including timely submission of any required report) or if FDA should uncover any failure to comply with federal, state, or local regulations related to narcotic treatment programs, CHP and Tennant must immediately and voluntarily surrender the Drug Enforcement Agency certificate of registration for each affected treatment program; FDA would then institute revocation action against CHP. The consent agreement also requires CHP to pay the costs of all future FDA inspections. (CDER)

Good Clinical Practices Draft Guideline Published. On August 17, FDA published a draft guideline, "Good Clinical Practice," prepared under the auspices of the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use. The draft guideline, currently at step 2 in the harmonization process, is intended to define "good clinical practice" and to provide a unified standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Step 2 involves collection of comments by the three regional regulatory agencies participating in ICH: FDA, the Ministry of Health from Japan, and the European Commission from the European Union. At step 3, regulatory agencies exchange these comments for incorporation into a harmonized guideline.

In October 1994 two guidelines reached step 4 of the harmonization process. They were the "Investigator's Brochure," which provides an agreed-upon format and content for the documentation of substances under clinical investigations, and the "Essential Study Document," which defines adequate documentation of the conduct of a clinical trial. At this step, the final draft goes to the Steering Committee for endorsement by the three regulatory parties to ICH and recommendation for adoption to the three regulatory bodies. (CDER)

Informed Consent for Patients Who Need Acute Emergency Care. On September 21 FDA published a proposed rule that would provide a narrow exception to existing requirements for obtaining and documenting informed consent in a limited class of research activities involving human subjects who, because of a life-threatening medical

condition, need emergency medical intervention, but [redacted] representative, cannot provide legally effective informed consent. (See "Appendix 5" for further source of information.) (CDER)

Consent Decree Signed. On September 8 H.E. Greene, president of Greene Welding and Supply, Incorporated, of Monroe, Louisiana, signed a consent decree of condemnation for compressed oxygen, USP. This company has a long history of violative inspections relating to GMP deficiencies. Despite the issuance of a warning letter, the company continued to operate without regard to GMP, and a seizure was recommended in early 1995. The seizure recommendation was approved and a magistrate judge ordered the corporation and Greene to post a bond and to satisfy all of the requirements set forth in the consent decree. (ORA)

GMP Workshop for the Medical Gas Industry Jointly Sponsored. FDA and the Florida Department of Health and Rehabilitation Services (HRS), sponsored a workshop for 125 representatives of the medical gas industry on July 18 in Orlando. The high violation rate in the medical gas industry in Florida prompted the district to develop the workshop to help industry comply with the current GMP regulations as they relate to the medical gases. Although the workshop was promoted only in Florida, industry representatives from Alabama, Kentucky, Missouri, Tennessee, and Texas also attended. The Florida HRS, which also has regulatory responsibility for medical gases, used the workshop as a training session for its staff who conduct inspections under Florida law. The Florida law and GMP requirements are modeled after the FD&C Act and the applicable *Code of Federal Regulations*. (ORA)

Generic Drug Evaluation

FDA Approves "First Generics". During the quarter FDA approved the following drug products: Roxane's Diclofenac Sodium Delayed-Release Tablets, 25 milligrams (mg), 50 mg, and 75 mg, equivalent to Voltaren by Geigy Pharmaceuticals; Zenith's Indapamide Tablets, 2.5 mg, equivalent to Lozol by Rhone Poulenc Rorer; NMC's Betamethasone Dipropionate Ointment USP (Augmented) 0.05 percent, equivalent to Diprolene AF by Schering Corporation; Watson's Butalbital, 50 mg, Aspirin, 325 mg, Caffeine, 40 mg, and Codeine Phosphate Capsules USP, 30 mg, equivalent to Fiorinal with Codeine #3 by Sandoz Pharmaceuticals; Novopharm's Glyburide Tablets, 1.25 mg, 2.5 mg, and 5 mg, equivalent to Micronase by Upjohn Company; Steris' Hydromorphone Hydrochloride Injections USP, 10 mg/mL, equivalent to Dilaudid-HP by Knoll Pharmaceutical Company; Roxane's Hydroxyurea Capsules USP, 500 mg, equivalent to Hyrea by E.R. Squibb and Sons, Incorporated; Sidmak's Protriptyline Hydrochloride Tablets USP, 5 mg and 10 mg, equivalent to Vivactil by Merck Sharp and Dohme; and Steris' Vecuronium Bromide for Injection, 10 mg and 20 mg, equivalent to Norcuron by Organon, Incorporated. (CDER)

FDA Hosts Meeting with Generic Industry Trade Associations. On July 14 FDA representatives met with representatives of the Generic Pharmaceutical Industry Association, the National Association of Pharmaceutical Manufacturers, the Nonprescription Drug Manufacturers Association, the National Pharmaceutical Association, and the Parenteral Drug Association to discuss the current status of the ICH's Multilateral Regulatory Group and ICH [redacted] approval Committee initiatives and the Office of Generic Drugs. (CDER)

[redacted] series of training [redacted] Manufacturing Division, Stonewall Plant, Elkton, Virginia, a large manufacturer of sterile bulk drugs. The Baltimore District Director, with representatives of the Baltimore compliance, investigations, and science branches, discussed such topics as GMP requirements of bulk pharmaceutical manufacturers, and compliance issues, validation requirements, FDA inspections, training of employees relating to GMP issues, the preapproval process for new drugs and preapproval inspections, the significance of the recent precedent-setting legal decisions, management's leadership role in quality assurance, and ways to respond effectively to an FDA inspection.

In 1993–94 Merck received three warning letters after inspections conducted at three manufacturing facilities found GMP deficiencies. The company's corrective action plan included the commitment to have all its personnel attend GMP training seminars given by Merck and FDA. Merck agreed to retrain all its U.S. manufacturing employees in GMP and validation requirements by September 28, 1995. (ORA)

Generic Applicants Can Now Use ICH Stability Requirements. On August 18 FDA informed all applicants for abbreviated new drug applications and abbreviated antibiotic drug applications that FDA would now accept ICH recommendations for long-term room-temperature conditions for stability studies. In addition, FDA explained the review priorities for bioequivalence study protocols for the Agency. (CDER)

New Drug Evaluation

Norplant Update. FDA and the manufacturer of Norplant contraceptive have recently developed information to help assure that patients are appropriately informed of the product's risks and benefits before implantation. In addition, the manufacturer has established a toll free telephone number (1–800–934–5556) where patients can obtain infor-

mation about Norplant and the names of providers who are experienced in the insertion and removal of Norplant.

Norplant, which was approved in 1990, consists of six silicone rubber capsules containing the hormone levonorgestrel. When surgically inserted under the skin of a woman's upper arm, the capsules provide contraceptive protection for up to 5 years. They are surgically removed at the end of that time, or earlier, if desired. Both insertion and removal are performed in the physician's office. (A talk paper was released on August 17, 1995; telephone 301–443–1130 for copies.) (CDER)

FDA Approves New Drug Therapy for Osteoporosis. Calcitonin salmon nasal spray to be marketed under the trade name Miacalcin Nasal Spray, was approved for the treatment of osteoporosis. The drug is approved for use by postmenopausal women, beginning 5 years after menopause. (A talk paper was released on August 18, 1995; telephone 301–443–3285 for copies.) (CDER)

FDA Approves Treatment of Impotence. Alprostadil injection, to be marketed under the trade name Caverject Sterile Powder, was approved for the treatment of erectile dysfunction due to neurologic, vascular, psychological, or

other diagnostic tests in the diagnosis of erectile dysfunction. (A talk paper was released on July 6; telephone 301–443–4177 for copies.) (CDER)

Androderm Approved for Testosterone Replacement. FDA approved Androderm (testosterone transdermal system) for testosterone replacement in hypogonadal men. This testosterone patch is much smaller than the already approved Testoderm. In addition, Androderm can be placed on the back, thighs, upper arms, and buttocks instead of the scrotum, as is specified for Testoderm. (CDER)

Fosamax Approved for Treatment of Osteoporosis. Only 6 months after the application was submitted FDA approved Fosamax (alendronate sodium) for the treatment of osteoporosis. This product represents a significant advance over other treatments (including Miacalcin Nasal Spray). (A talk paper was released on July 13; telephone 301–443–3285 for copies.) (CDER)

FDA Expands Access to Investigational Treatment for Cytomegalovirus (CMV) Retinitis. FDA authorized treatment investigational new drug status for intravenous cidofovir (Vistide) for human immunodeficiency virus (HIV)-infected persons with relapsing CMV retinitis that has progressed despite treatment. CMV retinitis is an eye infection that can lead to blindness in persons with impaired immune systems, as is the case with acquired immunodeficiency syndrome. (A talk paper was released on September 1; telephone 301–443–3285 for copies.) (CDER)

Unapproved New Drugs Ordered Destroyed. On September 18, a U.S. district judge entered a default decree of condemnation and destruction for $750,000 worth (retail value) of finished products seized on April 28 from Mallard Enterprises, Mobile, Alabama. The products were seized because they were deemed to be new drugs that lacked approved new drug applications, were not manufactured in accordance with GMPs, or contained unsafe color additives.

Mallard Enterprises has a long history of noncompliance with the law and applicable regulations. FDA issued a warning letter to the company on September 14, 1993, concerning its products "Baby Don't Be Bald" and "Retin A Cream," both unapproved new drugs. In 1994 the company repeatedly refused an FDA inspection, but FDA obtained a warrant and completed the inspection with the assistance of the U.S. Marshal's office. The hair treatment product was being manufactured at the time of the inspection. During that inspection it was noted that house paint and high strength universal tinting colorants for tinting latex, alkyl, acrylic, and oleoresinous paints were being added to some products. Labels did not accurately reflect the active ingredients, and there was general noncompliance with GMPs. Ten samples were collected for regulatory consideration during that inspection. (ORA)

OTC Drug Evaluation

OTC Drug Review Publications. During the quarter the Agency published one proposed rule, one final rule, and one partial stay of a final rule.

In the *Federal Register* of July 27 the Agency published a proposed amendment of the monograph for OTC bronchodilator drug products to remove the ingredients ephedrine, ephedrine hydrochloride, ephedrine sulfate, and racephedrine hydrochloride and to classify these ingredients as not generally recognized as safe and effective for OTC use. (See "Appendix 5" for source of additional information.)

In the *Federal Register* of July 27 the Agency published a final rule classifying any combination bronchodilator drug product containing theophylline as not safe and effective for OTC use. (See "Appendix 5" for source of additional information.)

In the *Federal Register* of August 16 the Agency published a partial stay of the final rule for topical OTC drug products for the prevention of swimmer's ear and for the drying of water-clogged ears that had been published on February 15, 1995. On the basis of new data that supported the use of 95 percent isopropyl alcohol in 5 percent anhydrous glycerin for the drying of water-clogged ears, the Agency stayed the August 15 effective date for the nonmonograph status of glycerin, anhydrous glycerin, and isopropyl alcohol for the drying of water-clogged ears. The Agency intends to amend the final monograph for OTC topical otic drug products to include conditions for the foregoing formulation for the drying of water-clogged ears. (CDER)

Prescription Drug Advertising and Labeling

FDA published a proposed rule in the *Federal Register* on August 24 (60 *FR* 44182–44252) for medication guide requirements for prescription drug product labeling for consumers. Inadequate access to appropriate information about their prescription medications is a major reason why patients err in using such medications; as a result they incur serious injuries and the health care system incurs substantial costs. (See "Appendix 5" for source of additional information.) (CDER)

Medical Devices and Radiological Health

Product Evaluation: Devices

FY 95 Medical Devices Progress Report. Faster reviews of most medical devices, more and speedier approvals for clinical studies of medical devices, and the near elimination of a backlog of devices awaiting review marked the FY 95 performance of the Center for Devices and Radiological Health (CDRH). These achievements continued a trend begun 2 years ago with the introduction of several management initiatives, including an expedited review process for life-saving devices and an abbreviated review process for low-risk devices.

The most striking acceleration of CDRH processes last year was achieved for devices in the 510(k) category. These devices, identified by the manufacturer as similar to already existing products, account for more than 90 percent of medical devices marketed in the United States. The average review time for 510(k)'s was reduced by more than 24 percent, from 182 days in FY 94 to 138 days in FY 95; more than half of the reviews of these devices that were completed in FY 95 took 91 days of less.

The backlog of 510(k)s under review for more than 90 days was reduced from 500 in October 1994 to 9 in October 1995. The virtual elimination of overdue applications will enable CDRH to start reviewing new 510(k) submissions almost immediately.

The average review time for premarket applications (PMAs) for new uses and new types of devices was reduced from 21.5 months in FY 94 to 20 months in FY 95. The 27 PMAs approved last year included the use of a catheter system through which an electric current destroys heart cells that cause abnormally fast heartbeats, and a mechanical blood vessel support inserted by a catheter to allow bloodflow to bypass a diseased liver, thus possibly avoiding major surgery.

Other approved devices regarded as a unique advance in diagnosis or treatment technology are lasers for smoothing corneas for some types of eye disease, a new way to use ultrasound to help broken bones heal faster, and a computerized pattern recognition device designed to improve quality control of PAP smear readings. By the end of FY 95, CDRH also cut by half the number of overdue PMA supplements—applications for modification of PMA devices—despite a 34 percent increase in this type of submission over the number in FY 94.

The proportion of investigational device exemptions (IDEs)—applications for proposed clinical studies of new devices—approved within 30 days of receipt increased from 30 percent in FY 94 to 65 percent in the second half of FY 95. In addition to speedier processing of IDEs, FDA cooperated in the development of an important new regulation that will provide Medicare coverage for patients in most device clinical trials.

In the coming year CDRH will work to further reduce the review time for PMAs and PMA supplements while maintaining its performance on 510(k)s and IDEs. (CDRH)

FDA Approves Liver Stent. On September 29 FDA approved a new, implantable medical device to prevent the recurrence of bleeding from veins in the esophagus of people with cirrhosis, a severe scarring of the liver caused by several different diseases. (A talk paper was released on September 29, 1995; telephone 301–443–3285 for copies.) (CDRH)

Surveillance and Enforcement: Devices

FDA Proposes Standard for Medical Device Wires. FDA has proposed setting a new performance standard for electrical wires that connect patients to medical devices such as those used to monitor breathing, heart rate, and brain waves.

A notice of the proposed standard appeared in the June 21 *Federal Register*. The standard is being proposed because of deaths and serious injuries that occurred when the wires, called cables and leads, were improperly connected. (A Talk Paper was released on July 5; telephone 301–443–3285 for copies.) (CDRH)

FDA Announces Informed Consent Proposals for Experimental Therapies. In the September 21 *Federal Register*, FDA proposed regulations to make it easier to study drugs and medical devices in patients who are in life-threatening situations and are unable to give informed consent for their use. The proposals are designed to clarify the rules for testing unapproved drugs and devices that may save lives and to provide safeguards for patients. (A Press Release was issued on September 21; telephone 301–443–3285 for copies.) (CDRH)

FDA Sponsored *In Vitro* Diagnostic (IVD) Workshop. The Baltimore District Office, in conjunction with the Baltimore Conference of the Central Atlantic States Association of Food and Drug Officials, the Center for Devices and Radiological Health (CDRH), and the Center for

Biologics Evaluation and Research, presented a 2–day *In Vitro* Diagnostic (IVD) Devices Regulatory Seminar. The program, which was held in Columbia, Maryland, attracted 60 participants from throughout the United States. Participants included industry representatives, investigators from Baltimore and New Jersey districts, and Agency representatives. Topics included good manufacturing practices for IVD manufacturers, process and method validation, complaint handling, investigation and analysis of failures, highlights of an FDA IVD inspection, pathways to successful device and biological licensed IVD submissions, CDRH review process initiatives, IVD compliance program guide on the commercialization of unapproved IVDs, FDA enforcement actions, and IVD recalls. (ORA)

Activities in Evaluating Examination Gloves. The Winchester Engineering and Analytic Center (WEAC) continues to test examination and surgeon's gloves for the Agency. This year WEAC has analyzed about 241 samples of glove barrier products, approximately 23 percent of which continue to be found actionable. WEAC also continues to support the overall glove analysis effort through the manufacture and shipment of glove analysis equipment and supplies to the laboratories in the other regions doing glove analyses, as well as serving as an information resource to the regional laboratories. (ORA)

WEAC Activities in Evaluating the Integrity of Latex Condoms. FDA has recently required manufacturers of condoms to provide assurance that their products have mechanical integrity as well as prevent leakage. To facilitate compliance monitoring under this directive, FDA made WEAC responsible for determining all of the necessary specifications for a specially designed automatic air inflation tester for condoms. Three automatic air inflation testers are now operating at WEAC, Southeast Regional [illegible] three laboratories will be responsible for all field testing (for water leakage and air inflation) of latex condoms. (ORA)

Final Life Energy Resources Defendant Sentenced. On September 22 a U.S. district court sentenced Pascal Ballistrea, the final defendant in the Life Energy Resources, Limited, case, to 41 months' incarceration followed by 3 years of supervised release. He was also ordered to pay a $275 special assessment.

Ballistrea had been charged with two counts of conspiracy to defraud FDA of its rightful function to regulate the REM SuperPro frequency generator and an unapproved new drug known as Miracle Cream. The indictment also charged Ballistrea with making false statement to the government about his distribution activities, and with violating the FD&C Act by causing the shipment of the two products into interstate commerce. In December 1994 Ballistrea was convicted of three felony and five misdemeanor counts for his part in the multitiered marketing scheme designed to promote and sell the REM SuperPro to cancer and acquired immunodeficiency syndrome patients. Sentencing was delayed while the judge considered various motions that Ballistrea filed. (ORA)

National Center for Toxicological Research

Integrated Research for Health Protection: NCTR

Scientific Research Goals Updated. Senior management, along with division and staff directors, recently updated the National Center for Toxicological Research (NCTR) mission statement and defined three strategic research goals that have been endorsed by the FDA/NCTR Science Advisory Board. NCTR's official mission statement as adopted is:

> The mission of NCTR is to conduct peer-reviewed scientific research that supports and anticipates the FDA's current and future regulatory needs. This involves fundamental and applied research specifically designed to define biological mechanisms of action underlying the toxicity of products regulated by the FDA. This research is aimed at understanding critical biological events in the expression of toxicity and at developing methods to improve assessment of human exposure, susceptibility, and risk.

According to NCTR's Director, the mission statement "articulates the vital role that NCTR plays in providing a strong scientific base upon which FDA can fulfill its central role of protecting public health."

NCTR's strategic research goals, as outlined to the FDA/NCTR SAB on May 9 and subsequently discussed with other FDA centers/Office of Regulatory Affairs staff, are as follows:

- *The Development of Knowledge Bases,* that is, accumulation of data that have predictive values extending beyond individual data elements and foster the identification of data gaps and new research areas leading to the development of predictive systems in support of regulatory decision making.
- *The Development of New Strategies for the Prediction of Toxicity,* that is, development of mechanism-based assays that contribute to a profile of information that supports a regulatory decision rather than the end-point, specific "yes/no" studies currently depended upon.
- The Conduct of Method-, Agent-, or Concept-Driven Research, that is, modification or development of better analytical and toxicological test methods, and the provision of data on specific agents of interest to FDA to facilitate current and anticipated Agency regulatory needs. (NCTR)

Methods Development for Regulatory Needs: NCTR

FDA Mass Spectrometry Symposium Addresses New Technologies and Challenges. On September 12–13 some 250 scientists from FDA, other federal agencies, academia, and industry met in Washington, D.C., to discuss major changes in the technology of mass spectrometry (MS) and their implications for FDA's scientific and regulatory activities. The scope and depth of the talks reflect the Agency's growing interest in applying both the proven and the newly developed techniques in mass spectrometry to regulatory research.

FDA's first major symposium on mass spectrometry, about 15 years ago, dealt with the significance to FDA and others of this technique's ability to detect vanishing small quantities of materials. The recent symposium, which included 22 technical presentations addressed both the use of new mass spectrometry techniques for regulatory measurements, and the growing capabilities of mass spectrometry for the study of biological events, including mechanistic-biology studies, cancer, and disease states. Among the lecturers were a University of Virginia representative who discussed mass spectrometry, intercellular communication, and disease states, and a Purdue University representative, who lectured on the development of ion-trap mass spectrometers.

One significant technological trend that was discussed is the use of tandem MS/MS structural characterization methods to study very small quantities of modified deoxyribonucleic acid (DNA) fragments resulting from carcinogenic interactions with the body's target tissue, DNA. This use of mass spectrometry demonstrates a capability that has important implications for FDA's ability to better understand the mechanisms of toxic action (in this example, carcinogenesis), thus assisting in moving away from the current dependence on end point observations (animal models).

The symposium also provided a forum in which FDA's Associate Commissioner for Science and the Senior Adviser for Science recognized the Center for Food Safety and Applied Nutrition's sustained superior achievement in regulatory mass spectrometry. This work established scientifically sound criteria that FDA adopted for both regulatory and research applications, to prove the identity of an analyte (a substance undergoing analysis) by mass spectrometry. In the ensuing 17 years, these criteria have proved to be a sound basis for the acceptance of mass spectral identifications in work submitted to FDA, as well as the required benchmark for proof of structure using mass spectrometry in regulatory decisions or scientific works published by FDA.

To encourage closer ties between the MS research community and FDA laboratories, FDA's Associate Commissioner for Science challenged the organizers to hold the next FDA mass spectrometry symposium within the next 3 years. He also affirmed the Agency's support of this discipline and noted that the symposium demonstrated anew the importance of having facilities dedicated to mass spectrometry within FDA. (NCTR)

FDA Scientists Investigate the Thermal Decomposition (Pyrolysis) of Bacteria. FDA scientists are using pyrolysis mass spectrometry with computerized pattern recognition (Py-MS + PattRec) to produce a pyrolysis mass spectrum for bacteria and to compare its spectral pattern with those of hundreds of other bacteria. Scientists lists can accomplish this comparison rapidly only by using a computer equipped with some form of pattern recognition software. This analytical technique promises to automate analyses and more rapidly identify possible pathogens in postmarket surveillance of food products.

Like a human fingerprint, the spectrum must be unique for each bacterial species, if one intends to use it to identify the microbe. Unlike a human fingerprint, a bacterial Py-MS spectrum varies with the medium on which it is cultured, the length of growing time before it is harvested for analysis, pyrolysis temperature and mass spectrometer acquisition parameters, and other factors. Each of these factors must be optimized and controlled in order to create a distinctive and reproducible "fingerprint."

The Army already uses this type of technology in the identification of biological agents for a limited group of species. The portable battlefield mass spectrometer uses a massive sampling device to gather many cubic yards of air in a few seconds and to concentrate the aerosol particles for analysis. Then the Army uses a very sophisticated two-stage mass spectrometer to give added specificity to the identification. For technical and economic reasons, this technique is not directly transferable into a food safety compliance context.

FDA scientists are upgrading two mass spectrometers and adapting the necessary pyrolysis sample inlets. They are using multiple mass spectrometers in order to demonstrate adequate control over the production of Py-MS fingerprints (i.e., to demonstrate that it is possible to compile a Py-MS data base analogous to the central library of FBI fingerprint records). First, the scientists must build a set of patterns for all likely species of foodborne bacteria on one spectrometer (MS#1), and then use a second instrument (MS#2) or several others to run the "unknowns." If, by consulting the MS#1 data base, one can accurately identify MS#2 unknowns, a technician in a remote FDA laboratory could culture swabs of food overnight, pyrolyze any colonies the next day on a PY-MS system, and determine whether or not the microbes were pathogens. The whole process is relatively cheap and rapid.

FDA scientists have already produced a usable Py-MS data base, which is essential for the practical implementation of Py-MS + PattRec for bacterial chemical classification in a compliance context. Other accomplishments to date include showing that the Py-MS patterns can separate bacteria into broad classifications familiar to microbiologists (e.g., gram positive and gram negative) and that similar bacteria are located close together on a graphic

factor plot. These results are reassuring to scientists familiar with the traditional series of tests used to categorize and identify bacteria.

Speed of analysis is a critical objective. Using manual sampling, mass spectrometer acquisition, and data treatment procedures, the Py-MS system is already able to identify an unknown sample in about 6 minutes. Even this excellent turn-around time can be improved later by automation. For comparison, another instrumental system based on capillary gas chromatography typically requires 45 minutes of instrument turn-around per sample and relatively labor-intensive sample preparation. (NCTR)

APPENDIX 1

Field Inspections, Samples Examined, and Wharf Examinations[1]

FY 95

Program Category	Establishment Inspections[2]		Domestic Samples Examined[3]		Import Samples Examined[4]		Wharf Exams[5]
	Classified[6]	Adverse Findings[7]	Classified[6]	Adverse Findings[8]	Classified[6]	Adverse Findings[8]	
Food and Cosmetics	5,741	2,309	12,431	1,650	23,253	7,788	33,172
Human Drugs	3,458	2,120	2,373	404	1,190	948	11,563
Biologics	2,267	852	4	1	60	34	47
Animal Drugs and Feeds	825	497	2,484	225	136	33	187
Medical Devices and Radiological Health	3,132	1,753	329	67	3,394	1,993	31,362
TOTALS[9]	15,011[10]	7,361	17,418[11]	2,350	28,007	10,783	76,331

1. Source of this data is the Office of Regulatory Resource Management, ORA.
2. ESTABLISHMENT INSPECTIONS: The number of different inspections made of establishments to determine if they are in compliance with the Acts enforced by FDA.
3. DOMESTIC SAMPLES EXAMINED: The number of samples of products of domestic origin (or of foreign origin if collected in domestic channels of trade) examined to determine compliance with Acts enforced by FDA.
4. IMPORT SALES EXAMINED: The number of samples of products of foreign origin in import channels of trade examined to determine whether the products are in compliance with the Acts enforced by FDA.
7. ADVERSE FINDINGS (ESTABLISHMENT INSPECTIONS): The number of classified establishment inspections where the district classification is either "Official Action Indicated" or one of the three subclassifications of "Voluntary Action Indicate" (as defined in Field Management Directive Number 86), based on the Acts enforced by FDA, policies of the Agency, and the compliance status of the observed establishment conditions at the times of inspection.
8. ADVERSE FINDINGS (SAMPLES ANALYZED): The number of analyzed samples which fail to meet established standards and policy guides, or would for other reasons support a regulatory action.
9. Totals may be different from the sum of the individual program categories because some establishment inspection may cover, and some samples may be analyzed under, more than one program area.

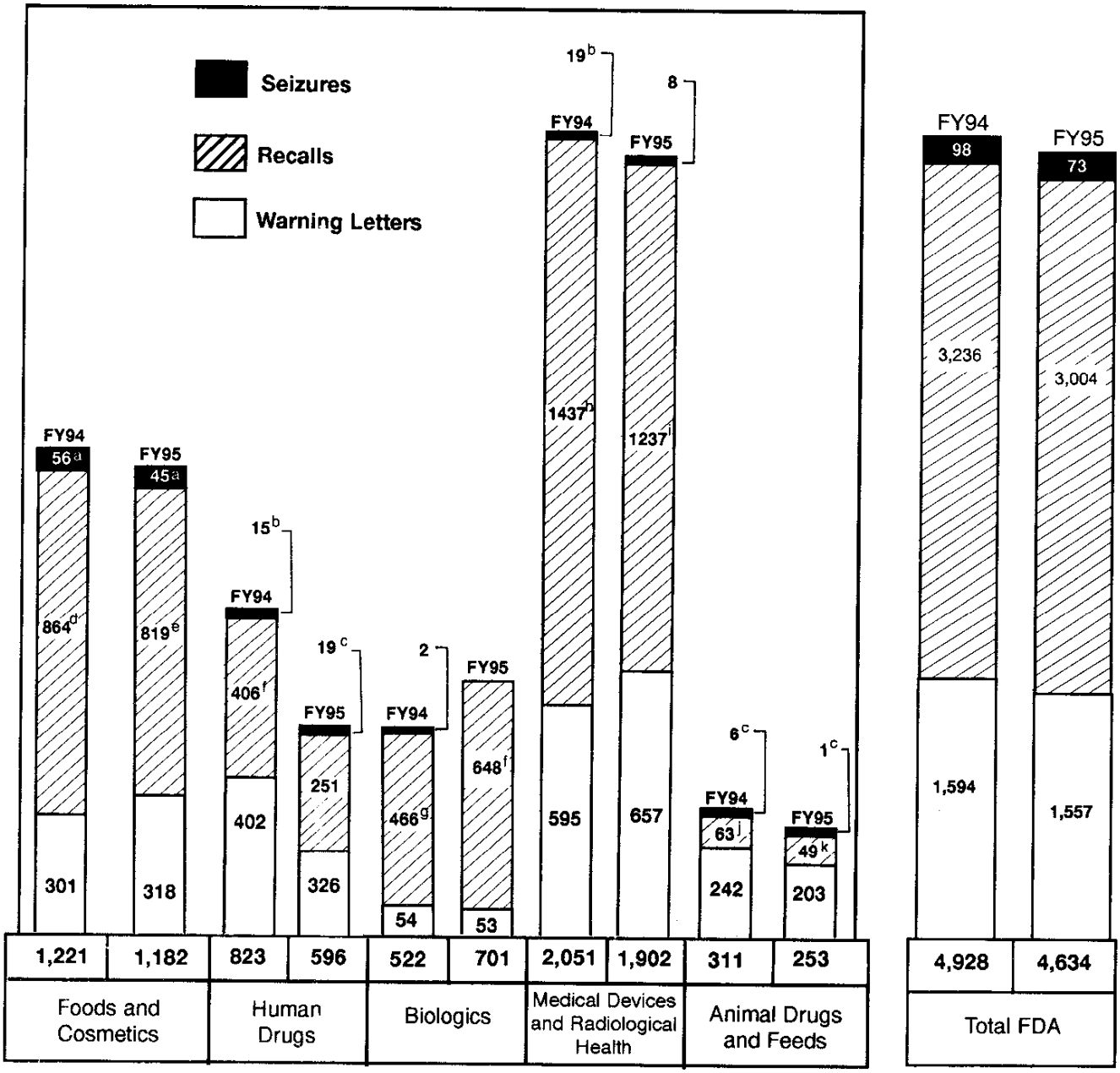
definition, all wharf examinations are classified in compliance.

6. CLASSIFIED: The number of establishment inspections or samples for which a decision has been made concerning the compliance status of the establishment or product.

ties, of which 3 were classified with adverse findings.

APPENDIX 2

Seizures, Recalls, and Warning Letters
FY 94 v. FY 95

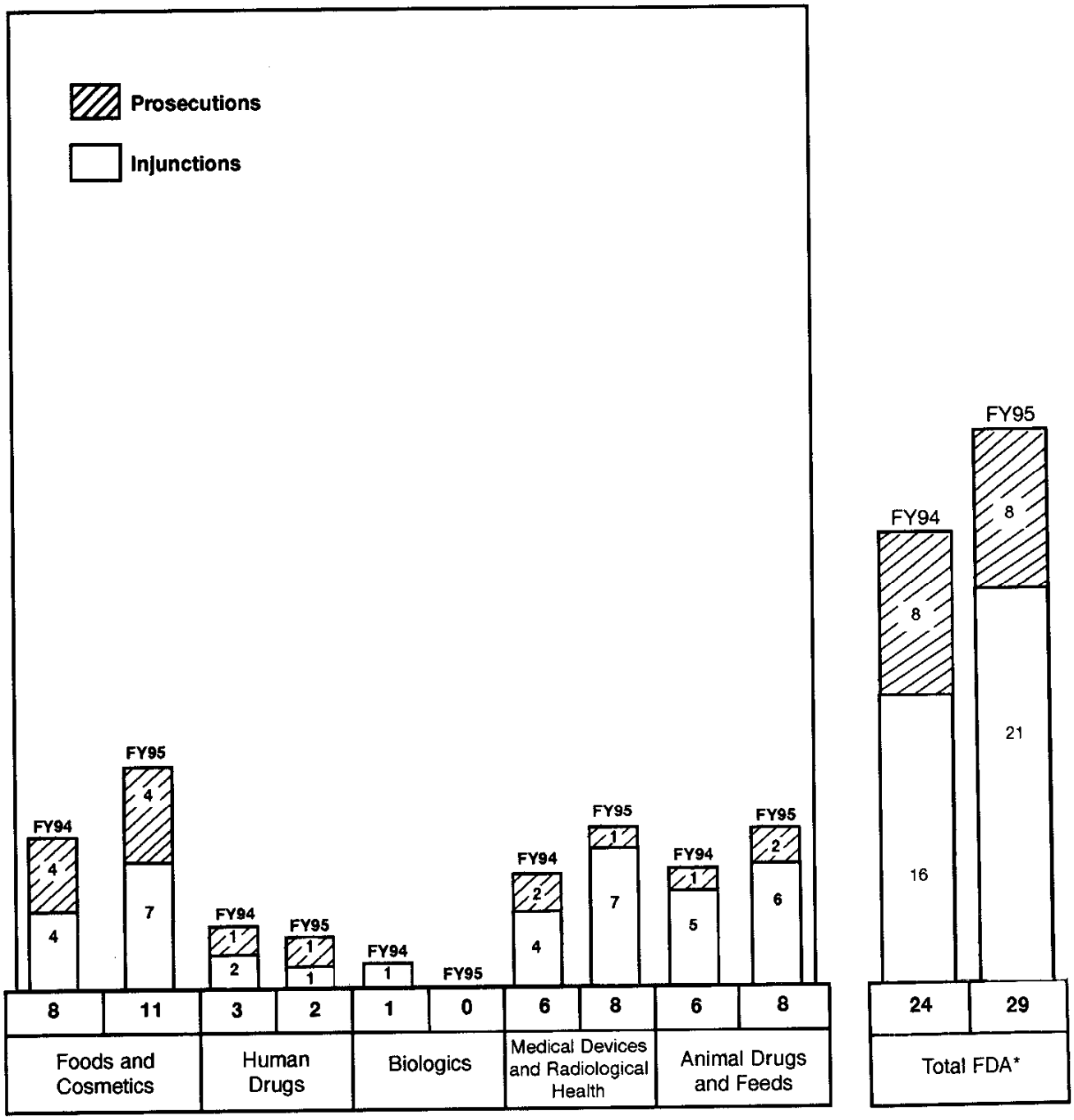


a. Includes 3 mass seizures
b. Includes 2 mass seizures
c. Includes 1 mass seizure
d. Includes 139 class I recalls
e. Includes 454 class I recalls
f. Includes 5 class I recalls
g. Includes 8 class I recalls
h. Includes 9 class I recalls
i. Includes 25 class I recalls
j. Includes 30 class I recalls
k. Includes 2 class I recalls

NOTE: Source of data is the Office of Regulatory Resource Management, and the Office of Enforcement, ORA.
Seizures—counted when approved by General Counsel.
Recalls—counted when approved by Centers.
Warning Letters—counted when issued.

APPENDIX 3

Prosecutions and Injunctions
FY 94 v. FY 95



*"Total FDA" statistics may be less than the sum of individual program statistics, because some enforcement actions affect more than one program.
NOTES: (1) Source of data is the Office of Enforcement, ORA. Counted when approved by General Counsel.
(2) FDA has detained 26,969 lots if imported products through the fourth quarter of FY 95.

APPENDIX 4

Congressional Testimony
4th Quarter FY 95

Date	Committee	Subject	Witness
August 1	House Committee on Government Reform and Oversight Subcommittee on Human Resources and Intergovernmental Relations	Silicon Breast Implants	David Kessler, M.D., Commissioner
September 14	House Committee on Government Reform and Oversight Subcommittee on Human Resources and Intergovernmental Relations	Policy Guidance Documents to FDA-Regulated Industry	William Schultz, Deputy Commissioner for Policy

NOTE: Source of data is the Office of Legislative Affairs.

APPENDIX 5

In the *Federal Register*

Notices Published. The following notices were among those published in the *Federal Register* during the quarter:

FDA Guidance Document Concerning Use of Pilot Manufacturing Facilities for the Development and Manufacture of Biological Products; Availability: FDA announced the availability of a guidance document for manufacturers of biological products to clarify the licensing requirements concerning the use of small-scale and pilot facilities to develop and manufacture biological products. The document is intended to clearly articulate that pilot facilities are eligible for licensure. (July 11)

Guideline for Quality Assurance in Blood Establishments; Availability: FDA announced the availability of a guideline intended to help manufacturers of blood and blood components including blood banks, blood centers, transfusion services, and plasmapheresis centers—to develop quality assurance (QA) programs that are consistent with recognized principles of QA and current good manufacturing practice (GMP). The emphasis of such QA programs is on preventing errors rather than on detecting them retrospectively. (July 14)

Statement Regarding the Demonstrations of Effectiveness of Human Drug Products and Devices: FDA announced its position regarding demonstrations of product effectiveness in new drug applications (NDAs) and premarket approval applications (PMAs). In evaluating NDAs and PMAs, FDA weighs the demonstrated effectiveness of a product against its risks, and considers other factors such as the seriousness and outcome of the disease being treated and the adequacy of existing treatments. The Agency does not require new human drug products or medical devices to be more effective than existing therapies, nor does it necessarily require the product to be compared with other products. For products intended to treat life-threatening diseases, diseases with irreversible morbidity, and contagious diseases that pose serious health risks to others, however, it is essential for public health protection that a new therapy be as effective as existing, approved therapies. (August 1)

Analysis Regarding FDA's Jurisdiction Over Nicotine-Containing Cigarettes and Smokeless Tobacco Products: FDA published a document titled "Nicotine in Cigarettes and Smokeless Tobacco Products is a Drug, and These Products Are Nicotine Delivery Devices under the Federal Food, Drug, and Cosmetic Act" and announced the availability of appendices to this document. (August 11)

Products for Human Use Derived from Transgenic Animals (1995); Availability: FDA announced the availability of a points to consider (PTC) document intended to help manufacturers produce safe, pure, potent, and effective therapeutic products for human use that are derived from transgenic animals (animals with an altered genome produced by introduction of deoxyribonucleic acid [DNA] through human intervention). (August 24)

Guide to Food Labeling Regulations Implementing the Nutrition Labeling and Education Act of 1990; Questions and Answers; Availability: FDA announced the availability of a document titled *Food Labeling, Questions and Answers, Volume II: A Guide for Restaurants and Other Retail Establishments*, which addresses various questions about the regulations that FDA issued to implement the Nutrition Labeling and Education Act of 1990 (the 1990 amendments). (September 19)

Investigational New Biological Product Trials; Procedure to Monitor Clinical Hold Process; Meeting of Review Committee and Request for Submissions. FDA announced a meeting planned for October, of the committee that reviews the clinical holds that the Center for Biologics Evaluation and Research (CBER) has placed on certain investigational new biological trials. FDA invited any interested biological company to use this confidential mechanism to submit to the committee for its review the name and number of any investigational new biological products trial placed on clinical hold during the past 12 months that the company wants the committee to review. (September 28) (OP/CBER)

Proposed Rules

Notices of Proposed Rulemaking Published. During the quarter FDA published the following notices of proposed rules and declarations in the *Federal Register* to inform interested persons of an opportunity to participate in rulemaking before the adoption of final rules:

Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for OTC Human Use; Proposed Amendment of Monograph for OTC Bronchodilator Drug Products: FDA proposed to amend the final monograph for over-the-counter (OTC) bronchodilator drug products to remove the ingredients ephedrine, ephedrine hydrochloride, ephedrine sulfate, and racephedrine hydrochloride and to classify these ingredients as not generally recognized as safe and effective (GRASE) for OTC use. This action was taken primarily in response to a request from the Drug Enforcement Administration to restrict OTC availability of

ephedrine because of its illicit use as the main substance used in the synthesis of the controlled substances methamphetamine and methcathinone. (July 27)

Regulations Restricting the Sale and Distribution of Cigarettes and Smokeless Tobacco Products to Protect Children and Adolescents: FDA proposed new regulations governing the sale and distribution of nicotine-containing cigarettes and smokeless tobacco products to children and adolescents to address the serious public health problems caused by the use of and addiction to these products. (August 11)

Prescription Drug Product Labeling; Medication Guide Requirements: Inadequate access to appropriate information on their prescription drugs is a major reason why patients use prescription medications inappropriately; this misuse results in serious personal injury and related costs to the health care system. FDA believes that it is essential for patients to receive adequate information with their prescription drugs. (August 24)

Protection of Human Subjects; Informed Consent: FDA proposed to amend its current informed consent regulations

search can proceed without obtaining informed consent. The regulation provides a narrow exception to the requirement for obtaining and documenting informed consent from each human subject before an experimental treatment begins. (September 21)

Prominence of Name of Distributor of Biological Products: FDA proposed to amend the labeling regulations to remove the requirement that the name of manufacturer be more prominent than that of the distributor, and to permit the names of distributors to be prominently displayed on biological product container labels, package labels, and labeling. (September 27) (OP/CBER/CDER)

Final Rules

Regulations Published: Among the regulations (documents having a legal effect most of which were codified in the *Code of Federal Regulations*) published during the quarter in the *Federal Register* were the following:

Food Additives; Threshold of Regulation for Substances Used in Food-Contact Articles: FDA amended its food additive regulations to establish a process for determining when the likelihood or extent of migration to food of a substance used in a food-contact article is so trivial as to require no regulation of the substance as a food additive. (July 17)

Bronchodilator Drug Products Containing Theophylline: FDA issued a final rule establishing that cough-cold combination drug products containing theophylline are not GRASE and are misbranded for OTC use. (July 27)

Medical Devices; Exemption from Premarket Notification for Certain Classified Devices: FDA exempted nine generic types of class I devices from the requirement of premarket notification. For the exempted devices FDA has determined that manufacturers' submissions of premarket notifications are unnecessary for the protection of the public health and that the Agency's review of such submissions will not advance its public health mission. (July 28)

Records and Reports Regulations for Radiation-Emitting Electronic Products: FDA amended its regulations regarding the requirements for recordkeeping and reporting of adverse experiences and other information relating to radiation-emitting electronic products. (September 19) (OP/CBER)

Hearings

officer. A *formal evidentiary hearing*, which is intended to resolve disputed factual issues, is conducted like a court trial and is generally held before an administrative law judge. The formal hearing process begins with publication of a *notice of hearing*. *Informal hearings* consist of opportunities for interested persons to present data, information, and views on matters pending before the Agency; they take place before designated Agency officials rather than administrative law judges. A *regulatory hearing* is a form of informal hearing.

The following list summarizes the status of administrative hearings as of this quarter. (The hearing clerk's reference number and the date of publication of the notice of hearing are given in parentheses.)

Formal Hearings

Milk, Lowfat Milk, and Skim Milk Standards: This hearing concerns the labeling of lowfat milk and skim milk to which milk solids have been added. The prehearing conference was held on November 9, 1983, and written direct testimony was filed on March 5, 1984. On September 17, 1984, the administrative law judge issued an initial decision against the position taken by the Center for Food Safety and Applied Nutrition (CFSAN). CFSAN filed exceptions on October 16 and the petitioners filed replies to the exceptions on November 2, 5, and 7. On November 28, 1984, CFSAN moved to strike an untimely exception filed

exceptions. (Docket Numbers 81N-204F, 76N-0175; October 6, 1983)

Vioform HC (Drug Efficacy Study Implementation [DESI]: This hearing concerns the Agency's proposed withdrawal of approval of Vioform Hydrocortisone cream, ointment, and lotion. The prehearing conference took place on November 7, 1984. Written direct testimony was filed on March 15, 1985, and supplemental written direct testimony was filed on September 20, 1985. Oral cross-examination was held between November 6 and December 4, 1985. Posthearing briefs and proposed findings of fact and conclusions of law were filed on March 3, 1986. On February 5, 1988, the administrative law judge issued an initial decision to withdraw approval of the drug. Exceptions were filed on April 6 and replies to exceptions were filed on June 6, 1988. The matter is now before the Office of the Commissioner for a final decision. (Docket Number 80N-0012; August 21, 1984)

Vasodilan (DESI): This hearing concerns the Agency's proposed withdrawal of approval of Vasodilan injection and tablets. The prehearing conference took place on December 5, 1984. Written direct testimony was submitted on April 29, 1985. Oral cross-examination was completed on July 18, and posthearing briefs were filed on September 20, were filed on October 22 and replies were filed on November 7, 1986. The matter is now before the Office of the Commissioner for a final decision. (Docket Number 84N-0167; September 28, 1984)

Cyclospasmol (DESI): This hearing concerns the Agency's proposed withdrawal of approval of Cyclospasmol. The hearing took place on June 18–27, 1985; posthearing briefs were filed on August 21, 1985. On September 25, 1986, the administrative law judge issued an initial decision to withdraw the drug. Exceptions were filed on November 24, 1986, and replies were filed on January 5, 1987. The matter is now before the Office of the Commissioner for a final decision. (Docket Number 89N–0168; October 18, 1984)

Mepergan Fortis Capsules (DESI): This hearing concerns the Agency's refusal to approve a supplemental application for Mepergan Fortis capsules. The prehearing conference was held on May 22, 1985. Written direct testimony was submitted on October 23, 1985. Oral cross-examination was completed on January 17, 1986, and posthearing briefs were filed on March 31, 1986. On December 4, 1987, the administrative law judge issued an initial decision finding that the drug had not been shown effective for the indication in question, and denied approval of the supplemental NDA. American Home Products filed exceptions on February 2, 1988, and the Center for Drug Evaluation and Research filed replies to exceptions on March 23, 1988. The matter is now before the Office of the Commissioner for a final decision. (Docket Number 81N–0080; December 31, 1984)

Pentaerythritol Tetranitrate (PETN) (DESI): This hearing concerns the Agency's proposed withdrawal of approval of the NDAs for certain single-entity coronary vasodilators containing PETN. The prehearing conference was held on February 2, 1988, and June 28 was the date for filing written direct testimony. Cross-examination took place between October 4 and 26, 1988, and briefs were submitted on December 19, 1988. On May 10, 1989, the administrative law judge issued an initial decision in which he found that PETN lacked substantial evidence of effectiveness. Exceptions were filed on July 10 and replies to these exceptions were filed on September 8, 1989. The matter is now before the Office of the Commissioner for a final

Public Hearing Before the Commissioner

Sulfamethazine: On May 25–26, 1988, FDA held a public hearing before Commissioner Young. The hearing provided an opportunity for interested persons to present scientific data and information on the safety of the new animal drug sulfamethazine, particularly with respect to whether it can be used in food-producing animals without leaving illegal drug residues in tissue. FDA will use the information presented at the hearing, with other relevant data, to determine whether the use of sulfamethazine in food-producing animals presents an unacceptable risk to human health and if so, what course of action would be appropriate to minimize that risk.

The National Toxicology Program has completed its review of two sulfamethazine feeding studies on mice and rats that were conducted by the National Center for Toxicological Research (NCTR). NCTR's final reports on these studies have been reviewed by the Center for Veterinary Medicine, which is preparing a notice of opportunity for a hearing on a proposal to withdraw approval of sulfamethazine. (GC)

APPENDIX 6

Distribution of FDA Personnel In Terms of Full-Time Equivalents (FTEs)* As of September 30, 1995

Organization	Expended To Date	Ceiling For Fiscal Year	Difference: Projected v. Ceiling
Office of Commissioner**	140.5	151.0	(10.5)
Office of Policy	34.6	38.0	(3.4)
Office of Operations/Immed. Office	8.6	7.0	1.6
Office of Orphan Product Development	22.5	18.0	4.5
Office of Regulatory Affairs	3,376.4	3,360.0	16.4
Center for Biologics Evaluation and Research	808.8	870.0	(61.2)
Center for Drug Evaluation and Research	1,549.7	1,608.0	(58.3)
Center for Devices and Radiological Health	1,108.8	1,116.0	(7.2)
Center for Food Safety and Applied Nutrition	871.2	868.0	3.2
Center for Veterinary Medicine	266.8	270.0	(3.2)
National Center for Toxicological Research	243.1	245.0	(1.9)
Office of External Affairs/Immed. Office	15.4	13.0	2.4
Office of Health Affairs	37.8	39.0	(1.2)
Office of Legislative Affairs	31.8	33.0	(1.2)
Office of Management & Systems/Immed. Office	13.4	15.0	(1.6)
Office of Planning and Evaluation	44.0	48.0	(4.0)
Office of Information Resources Management	59.3	75.0	(15.7)
OIRM/PCC	113.5	121.0	(7.5)
Office of Management	499.1	500.0	(0.9)
Totals	9,355.4	9,512.0	(156.6)

*Data provided by the Division of Financial Management, Office of Management.

**Office of Commissioner	*Expended To Date*	*Ceiling*
Immediate Office	32	27
Equal Opportunity Office	21	20
Office of Special Investigations	0	7
Office of Chief Counsel	67	76
Office of Executive Secretary	20	21

End-of-Year
Review and Monitoring Activities

The charts below summarize select review and monitoring activities from the Agency's various program areas. This appendix is published once each year in the fourth quarter edition of the FDA Quarterly Activities Report.

Animal Drugs and Feeds

New Animal Drug Applications

	FY 93	FY 94	FY 95
Originals received	39	30	20
Resubmissions	112	78	55
Actions	143	135	90
Approved	(18)	(32)	(31)
Incomplete [1]	(125)	(103)	(59)
Pending [2]	64	51	36
Amendments [3]	123	139	83

Investigational New Animal Drug Applications

	FY 93	FY 94	FY 95
Applications received	4,326	5,094	4,593
Actions [5]	4,058	5,246	4,639
Pending	756	621	574

Adverse Drug Reaction Reports

	FY 93	FY 94	FY 95
Received	1,501	1,603	2,605
Animals involved	29,499	105,500	55,539

New Animal Drug Application Supplements

	FY 93	FY 94	FY 95
Originals received	464	749	1,071
Resubmissions	217	193	197
Total actions [4]	545	799	1,207
Pending [2]	239	381	443
Amendments	133	206	270

Related Correspondence

	FY 93	FY 94	FY 95
Received	347	434	638
Actions	320	423	596
Pending	72	80	129

1. An incomplete application has deficiencies that must be resolved before the application can be approved.
2. Pending refers to applications without final action at the end of each fiscal year.
3. Figures from FY 93 and later are based on a new tracking system which defines some categories of work differently than in previous years. "Amendments" are sponsor submitted changes to applications while under review in the Center. "Related correspondence" is defined as other forms of correspondence from the new animal drug applicant, such as meetings, general discussions, comments, and clarifications.
4. Actions include approvals and incomplete supplements. An incomplete supplement to an application has deficiencies that must be resolved before the application can be approved.
5. Actions include authorizations and acknowledgements. An authorization is issued by FDA to allow meat, milk, and eggs derived from food producing animals treated with an investigational new animal drug to be used for food. Acknowledgements are other forms of correspondence sent to an investigational new animal drug applicant regarding a study protocol, safety and efficacy data, or other information submitted to an investigational new animal drug file.

NOTE: Source of data is the Center for Veterinary Medicine.

Biologics

Biological Licensing Activities

Two licenses are necessary to manufacture and distribute a biological product. One license is for the product and the other is for the establishment in which it is produced. Supplements to licenses are required for any significant change.

	Establishment			Product		
	FY 93	FY 94	FY 95	FY 93	FY 94	FY 95
Applications received [1]	8	19	20	39	39	50
Licenses issued [2]	17	10	22	55	24	58
Supplements completed [3]	267	285	437	635	671	1,003

Biological Investigational New Drug Applications

	FY 93	FY 94	FY 95
Originals received	527	503	536
Amendments received and reviewed	8,100	9,238	9,882
Active INDs [4]	2,967	2,752	2,804

1. Reference numbers assigned during fiscal year.
2. New licenses issued.
3. Includes approved, withdrawn, inactivated, or denied or refused to file.
4. Active investigational new drug applications (INDs), are those that are neither terminated nor discontinued but are still under active investigation.

NOTE: Source of data is the Center for Biologics Evaluation and Research.

Food Safety and Cosmetics

Food Additives Petitions

	FY 93	FY 94	FY 95
Receipts [1]	56	30	48
Actions [2]	47	49	48
In review status end of period	255	243	239
Awaiting action over 180 days	(80)	(70)	(78)

Color Certification

	FY 93	FY 94	FY 95
Approved	3,711	3,980	4,101
Rejected	41	49	31

Food Labeling Small Business Exemption

	FY 93	FY 94	FY 95
New Firms	[3]	6,440	2,174
Renewals	[3]	[4]	4,136

1. *Receipts include the number of the new food additive petitions received during the year plus any reinstated petitions that had been previously dropped.*
2. Actions include the number of food additive petitions that either have been approved or that have been withdrawn, dropped, or denied.
3. Not Applicable. The small business exemption legislation did not take effect until May 1994.
4. Small business exemptions are renewed on an annual basis each May. The small business exemption legislation was not effective until May 1994 making the first renewals due in May 1995 (fiscal year 1995).

NOTE: Source of data is the Center for Food Safety and Applied Nutrition.

Medical Devices and Radiological Health [1]

Medical Device Premarket Approval Applications

	FY 93	FY 94	FY 95
Receipts	40	43	39
Completions	54	54	58
Approvals	(24)	(26)	(27)
Other [2]	(30)	(28)	(31)
Total PMA actions [3]	323	354	249
Under review at end of year	150	139	125
Under active review	(94)	(67)	(69)
On hold [4]	(56)	(72)	(56)
Awaiting cycle decision past 180 days	45	22	26

Medical Device Premarket Approval Applications Supplements

	FY 93	FY 94	FY 95
Receipts	394	372	499
Completions	415	461	514
Approvals	(354)	(385)	(435)
Other [5]	(61)	(76)	(79)
Total PMA supplement actions [6]	832	809	744
Under review at end of year	465	376	377
Under active review	(364)	(243)	(226)
On hold [4]	(119)	(133)	(151)
Awaiting cycle decision past 180 days	173	110	49

Medical Device Premarket Notifications [510(k)s]

	FY 93	FY 94	FY 95
Receipts	6,288	6,434	6,056
Completions	5,073	7,135	7,980
Substantially equivalent	(4,007)	(5,498)	(5,594)
Not substantially equivalent [7]	(135)	(135)	(101)
Other [8]	(931)	(1,502)	(2,285)

Investigational Device Exemptions Applications

	FY 93	FY 94	FY 95
Receipts	241	171	214
Completions	248	174	210

Medical Device Reports

	FY 93	FY 94	FY 95
MEDWatch Mandatory Reporting Program			
Manufacturer reports:			
Malfunctions	28,663	30,911	28,971
Serious injuries	50,637	72,723	52,531
Deaths	1,266	1,582	1,770
Other reports	26	31	22
User facility reports [9]	2,325	2,411	3,323
Distributor reports [9]	1,121	1,274	1,759
MEDWatch Voluntary Reporting Program [10]	3,690	3,985	3,806
Recall reports [9]	436	545	507
Total received	88,164	113,462	92,689

1. All data are preliminary. Numbers may vary from year to year due to deletion of duplicate reports, receipt of additional information allowing "other" reports to be recategorized, and resolution of incomplete or problematic reports.

2. Includes actions that did not result in an approval/disapproval decision, such as a sponsor directed hold, reclassification of the device and conversion of the PMA to another regulatory category, and official correspondence concerning the abandonment or withdrawal of the PMA, placing the PMA on hold, and other miscellaneous administrative actions.

3. Includes all actions taken on PMAs throughout the year: filing decisions, review activities, and review decisions, which include approval, approvable, not approvable, and denial.

4. FDA processing of an application "on hold" is officially suspended until the applicant provides additional information necessary for a decision.

5. Includes actions that did not result in an approvable/disapproval decision, such as a sponsor directed hold, reclassification of the device and conversion of the PMA supplement to another regulatory category, and official correspondence concerning the abandonment or withdrawal of the supplement, the status of the supplement as a special or 30 day submission, and other miscellaneous administrative actions.

6. Includes all actions taken on PMA supplements throughout the year: panel track filing decisions, review activities, and review decisions, which include panel track approval, nonpanel track approval, approvable, and not approvable.

7. If FDA determines a devices is "not substantially equivalent" to an eligible existing device, it is automatically placed in class III and cannot be marketed until the device is reclassified or the manufacturer submits, and FDA approves, a premarket approval application.

8. Includes final administrative actions that did not result in a substantially equivalent/not substantially equivalent decision because the 510(k) or device/product was: withdrawn by the applicant, deleted due to lack of response, a duplicate, not a device, a transitional device, regulated by CBER, a general purpose article, exempted by regulation, and other miscellaneous actions.

9. New reporting requirement established by the Safe Medical Devices Act of 1990.

10. Effective June 3, 1993, the former Problem Reporting Program (PRP) became part of the MEDWatch Voluntary Reporting Program.

NOTE: Source of data is the Center for Devices and Radiological Health.

Human Drugs

New Drug Applications

A new drug application (NDA) must be submitted to FDA by an applicant who wishes to market a new drug. FDA must approve the application before the drug can be marketed in the United States. An active moiety that has never been previously marketed or approved in the United States for use in a drug product either as a single ingredient or part of a combination is a new molecular entity (NME).

	FY 93	FY 94	FY 95
Originals submitted [1]	97	128	140
Filed [2]	84	93	108
Refusals to File	25	16	11
Review actions[3]:			
Approved	83	62	71
NMEs approved	(26)	(24)	(26)
Approvable [4]	45	42	57
Not approvable [5]	50	48	52
Pending [6]	174	182	155
Overdue [7]	31	38	14

Investigational New Drug Applications

An investigational new drug (IND) is a new drug or antibiotic drug that is to be used in a clinical investigation. A commercial IND is submitted by a sponsor with the intent to gather data to eventually support an NDA. A research IND is submitted by a sponsor whose main intent is to advance scientific knowledge by using the drug as a research tool for early clinical investigation.

	FY 93	FY 94	FY 95
Originals received	2,413	2,223	1,972
Commercial	(381)	(360)	(358)
Research	(2,032)	(1,863)	(1,614)
Active INDs [8]	10,682	11,171	11,678

Abbreviated New Drug Application [11]

The Drug Price Competition and Patent Term Restoration Act of 1984 amended the FD&C Act to allow ANDAs for drug products first approved after 1962. This Act greatly expanded the universe of drug products for which generic equivalents could be available. ANDAs are accepted by FDA for drug products identical to an approved listed drug, acceptably similar, or related to the drug products in the Drug Efficacy Study. In addition, ANDAs are accepted for allowable variations to listed drug products which are the subject of an approved suitability petition approved after 1962 which have been judged to have effective indications.

	FY 93	FY 94	FY 95
Receipts [12]	1,593	1,503	1,604
Original receipts	(308)	(332)	(404)
Actions [13]	1,177	1,216	1,215
Approved	(215)	(255)	(288)
Withdrawals received [14]	929	565	516
Approved	(422)	(257)	(193)
Unapproved	(507)	(308)	(323)

NDA Effectiveness Supplements

An effectiveness supplement to an NDA is a proposal by the applicant to modify the "approved effectiveness" (i.e., indication, dosage regimen, route of administration, or size of the patient population) in the labeling of an already approved drug product.

	FY 93	FY 94	FY 95
Submitted [9]	76	105	93
Approved [10]	54	50	61
Pending [5]	102	134	107
Overdue [6]	58	59	37

Adverse Drug Reaction Reports

	FY 93	FY 94	FY 95
Received	149,015	147,055	133,384
Evaluated	149,015	147,055	133,384

1. Beginning in FY 94, "originals submitted" includes original submissions and submissions following refusals to file, withdrawal or unacceptable for filing actions. Type 6 NDAs (new indications for previously approved or marketed drug products) are now counted as effectiveness supplements.
2. Filed includes the number of NDAs that are pending filing (applications received but not yet officially filed).
3. Review actions are the number of actions (approved, approvable, not approvable) that occurred in the fiscal year regardless of when the NDAs were received.
4. An "approvable" action letter is issued by FDA when an application has substantially met FDA requirements, but minor issues remain that still must be resolved before the application can be approved.
5. A "not approvable" action letter is issued by FDA when an application has major deficiencies.
6. Pending refers to the pool of applications/supplements without a review action at the end of the fiscal year. Any one application/supplement could have been in the pool for several years.
7. Overdue refers to applications/supplements that are pending beyond the due date. For user fee applications (those received on or before 9/1/92), the due date is the user feel goal date (12 months with a one-time allowable extension of 3 months of the goal date). For pre-user fee applications, the due date is the regulatory due date (180-day clock with extensions for major amendments).
8. Active INDs are those that are neither inactivated nor withdrawn but are still under active investigation.
9. Beginning in FY94, "submitted" includes original efficacy supplement submissions, submissions following refusals to file, withdrawal or unacceptable for filing actions, and Type 6 NDAs. In FY95, "submitted" also includes labeling supplements containing clinical data.
10. In FY94, Type 6 NDAs were included in approved counts. In FY95, labeling supplements with clinical data were also included in the counts.
11. Abbreviated antibiotic drug applications (AADAs) and ANDAs were combined beginning in FY 90.
12. Receipts include originals and resubmissions. 13. Actions include approvals.
14. Withdrawals reflect requests by applicants to "withdraw" their abbreviated applications from FDA either prior to approval (Unapproved) or subsequent to approval (Approved). The applicant will cease marketing of the product when the application is withdrawn subsequent to approval.

NOTE: Source of data is the Center for Drug Evaluation and Research.

* U.S. G.P.O.:1996-404-915:40001